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Yellow Fever: The Complete Symposium

YELLOW FEVER

A SYMPOSIUM IN COMMEMORATION OF CARLOS JUAN FINLAY

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THE JEFFERSON MEDICAL COLLEGE of PHILADELPHIA

22-23 SEPTEMBER

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The addresses in this symposium

were designated as

William Potter Memorial Lectures

Mr. Potter was a member of the Board of Trustees of the Jefferson Medical College from 1894-1926 and its president from 1897-1926.

YELLOW FEVER

A Symposium in Commemoration of

Carlos Juan Finlay

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These meetings were arranged in cooperation with officials of the Republic of Cuba and with officers of the Pan American Sanitary Bureau. It was the general feeling that the most appropriate tribute to Carlos Finlay would be found in an authoritative conference on yellow fever, a subject to which Finlay was completely dedicated.

Carlos J. Finlay, M. D. — 1833 - 1915

Class of 1855, Jefferson Medical College

Carlos J. Finlay was born in Camaguey, Cuba, in 1833. His father was a Scotch physician, his mother was French. His early education was by private tutor. At the age of eleven he was sent abroad for schooling in France and in Germany. The process of education was frequently interrupted by illness but he achieved a solid foundation in the classics, history, mathematics, geography, physics, and languages. For the latter he had great facility and insisted upon this all of his life — breakfast was always in Spanish, lunch in English, and dinner in French. Presumably, he reserved German for certain other periods.

In 1853, at the age of 20, Carlos Finlay came to Philadelphia with his uncle, Philip de Barrès, and both registered at the Jefferson Medical College. But Finlay signed with the name Charles and on October 27th paid the matriculation fee of $5, and the course fee of $15. On the 17th of October, 1854, he registered for his second year. At that time he paid another fee of $15 and indicated that his preceptor was S. W. Mitchell. In reality he was the first pupil of Weir Mitchell and his first disciple. This was the beginning of their life-long friendship. He received his doctor's degree on March 10, 1855. No record of his thesis has been found.

Following his graduation he evidently spent an additional year with Weir Mitchell in Philadelphia but in 1856 he began a series of travels, which included a period in Paris of postgraduate study in ophthalmology. He finally began permanently to practice medicine in Havana in 1864. His great interest in epidemiology and public health began in 1867 when Havana suffered from a severe epidemic of cholera. His logical reasoning showed that the disease was water-borne and he traced one phase of the epidemic to the original case. His views were, however, so opposed to those of the time that his communication was refused publication.

During the next few years he undertook to investigate the matter of yellow fever in spite of his busy practice. The basic equipment was the microscope which he had brought from Philadelphia. His long series of publications on yellow fever began in 1872. In due course he became established as a foremost authority on this disease, first officially recognized in 1879 when the Governor General appointed him to cooperate with the United States Commission on Yellow Fever. He served several similar appointments in the following years; perhaps the most notable was as Chairman of the Yellow Fever Board organized in 1899 by the provisional government of Cuba. This group worked closely with the United States Army Board headed by Walter Reed.

In 1902, at the end of the occupation, Finlay became Chief Sanitary Officer of Cuba—a position from which he retired in 1909 at the age of 76.

In February 1881, as a representative of Cuba and Puerto Rico to the International Sanitary Conference in Washington, Finlay first presented his argument as to the necessity of an intermediate agent to explain the transmission of yellow fever. This idea was completely original, independent, and thoroughly heretical. In August of the same year, Finlay declared the vector to be the mosquito now known as *Aëdes aegypti*. Prior to the latter announcement Finlay had undertaken the experimental inoculation of informed volunteers by the use of infected mosquitos. He believed that he succeeded in these first attempts. His subsequent attempts (the total amounted to 102 during twenty years) were perhaps less convincing. In retrospect it is almost impossible to evaluate these experiments, for the difficulties in clinical diagnosis were then, as now, enormous. Certainly the theory was completely established by the work of the Army Board headed by Walter Reed. No reader of Finlay's original reports can escape the idea that this extraordinary man, without resources and without the spiritual support of his colleagues at the time, actually managed a very considerable affair of much daring and of enormous originality. Considering the state of knowledge of those times this man stood far ahead.

Although history has marked Finlay for his work on yellow fever, his interests were wide. He made significant contributions in the fields of leprosy, beriberi, filariasis, trichinosis, relapsing fever, cholera, tuberculosis, and many other topics.

Finlay was rather firm in his convictions. During twenty years he gained only one follower for his mosquito theory but he continued to proclaim it at every opportunity and was considered something of a crank. He added to his reputation as a determined individual when at the age of 65 he joined the American Army as a Contract Surgeon and undertook active duty with the troops in Cuba.

Jefferson Medical College recognized the quality of Finlay and his work by awarding him the honorary degree of Doctor of Science in 1902. It was also at about this time that he was proposed by his friend, Weir Mitchell, for honorary fellowship in the College of Physicians of Philadelphia. He received many honors in his lifetime from many nations and from many scientific bodies.

Carlos Finlay died on August 20th, 1915. By that time he had become a hero. The ensuing years have dealt well with the man and with his work. There is a Finlay Institute in Havana, a Laboratorio Carlos Finlay in Panama, a Finlay Institute in Colombia. There are Finlay streets in various cities. The Pan American Medical Congress celebrates Finlay's birthday, December 3rd, as the official Day of American Medicine. The commemoration of the centenary of Finlay's graduation is a proud time, for Jefferson is greatly honored by its relationship to the "poor practitioner" who became a prophet.

Welcome

William Potter Wear

Mr. William Potter Wear, a member of the Board of Trustees of the Jefferson Medical College of Philadelphia, is the grandson of Mr. William Potter, a member of the Board of Trustees from 1894-1926 and its president from 1897-1926, in whose honor the addresses in this symposium are designated as William Potter Memorial Lectures.

Muy distinguidos señores:

Tengo gran placer en darle a ustedes la bienvenida a Jefferson. Es un gran honor para Jefferson el rendir tributo a la memoria del distinguido hombre que fué Carlos Finlay.

Hace muchos años que no hablo el español y espero me perdonen ustedes mis faltas de gramática, pero quiero hablarles en vuestra propia lengua.

Ladies and Gentlemen:

Jefferson is proud to honor the memory of such a distinguished man as Carlos Finlay. Jefferson is also proud of having so many distinguished visitors here today and on behalf of the Board of Trustees I wish to tell you how pleased we are to have you with us on this occasion.

To our Cuban friends I wish to say *saludos amigos.*

CONTENTS

Symposium on Yellow Fever

McClellan Hall, Jefferson Medical College

Chairman: *Dr. Fred L. Soper (Washington)*

THE EARLY HISTORY OF YELLOW FEVER

DR. PEDRO NOGUEIRA

Outstanding authority in the field of preventive medicine and public health in Cuba. His avocation for many years has been the history of yellow fever. Chiefly instrumental in bringing about the erection of the monument to the heroes of the yellow fever experiments at the site of Camp Lazear.

It is quite fortunate that posterity, which will never again experience this abyss of pain, may regard our narrative as a fable. Thus wrote Petrarch with reference to the plague epidemic in Florence in 1348. The gay adventurers who first explored America may have regarded yellow fever in a similar light. It was an affliction which took lives indiscriminately and mysteriously. Certainly for centuries it appeared that the treasures of the tropics were guarded and protected by a monster. Yellow fever maintained its threat.

What can be said of the origin of yellow fever? There are two schools of thought. The first theory is that the disease and its urban vector were imported to the Americas from the Guinea coast of Africa. The second possibility, and to this the writer adheres, is that this pestilence had existed endemically in the Americas, perhaps for untold time before the Conquest.

Yellow fever did not originate in Europe. Hippocrates does not mention it. There are no descriptions of this striking disease entity by any European writer of the Pre-Columbian period. It surely did not originate in Africa as believed by Audourd and Carter. The nationals of several European countries visited the west coast of Africa, nowadays an endemic area, but no description of this disease was recorded. If such a disease had been encountered, the writers of those days would have mentioned it. Neither did the Portuguese navigators, such as Bartholome Diaz, Albuquerque, or others, refer to it.

In 1879, J. Jones (Proceedings of the Louisiana State Association, p. 59) was unable to find the disease or its symptoms in the works of Herodotus, Strato, Cornelius, Justin, Virgil, Floro, Veleyo Paterculo, Caesar, Horace, Cicero, Xenophon and Tacitus. Nothing about yellow fever appeared in the papers of the writers of the Middle Ages until the discovery of America. Finally, the American origin of the disease is supported by the discovery of jungle yellow fever in South America.

Ancient Times

The study of the Mayan codices "CHUMAYEL" and "TIZIMIN," made by the Bishop of Yucatan, Crescencio Carrillo Ancora, proves beyond all

doubt — as pointed out by Finlay in his 1897 paper "CONFORMITY BETWEEN THE PHILOLOGY AND THE HISTORY OF YELLOW FEVER" —that before the discovery there were epidemics of yellow fever, or of "Black Vomit," in the coastal areas of Central America. As described by Carrillo, in folios 16 and 17 of the Tizimin Codex, handed down to us by the Indians of Tizimincah, there is a note on the fourth epidemic of black vomit in Yucatan in 1648, which conforms with what is described in the Chumayel Codex. The writer pointed out there is no other report of the disease until that year. Since the peninsula was not discovered until 1517, it must be concluded that the other three epidemics were suffered before 1517.

The first accurate description of yellow fever seems to be the one written in the year 1495, after the battle known as Vega Real or Santo Cerro, fought by Columbus in Hispaniola against the Indians. After that, the expeditions of Ovando, Nicueza, Hojeda et al., ended in dreadful disasters. There can be no doubt that before that battle yellow fever exerted its lethal influence in the Antilles and in the Spanish Mainland under the names of MODORRA, MODORRA PESTILENCIAL and FIEBRE MALIGNA PUTRIDA; in Mexico under the names of PESTE and PESTILENCIAS, MATZLAHUATT and COCOLITZLE; in Yucatan under the name of XEKIK, and among the Caribbeans under the name of POULICANTINA.

Santo Domingo was scourged in 1495 and later in 1554, 1560, 1567, 1580, 1583 and 1588, the last named date coinciding with the expedition of the pirate Drake which was totally annihilated. According to the Spanish writers Hernandez Morejon and Hurtado de Mendoza, Cadiz and Malaga were visited in 1507 and 1582.

17th and 18th Centuries

In the year 1635 the Island of Guadeloupe was scourged. There is a superb description of this epidemic by Father Dutertre. There was a second attack in 1648 when the epidemic reached Yucatan.

The Island of Cuba, a land favored by nature, was the most beautiful possession of the Spanish Crown, as it has all the necessary means which make for human happiness. Bathed by the Caribbean Sea, it sparkled in the distance as an emerald carved in a silver setting, and it served as a trading center to several world powers, thus being favored by great immigration currents. However, as if everywhere God wanted to remind man of his misfortunes, the cup of bitterness being behind apparent happiness, He placed among the delights of this paradise the exterminating disease of the Black Vomit. According to Pezuela, in the year 1649 our country "was pitilessly attacked by an unknown and horrible epidemic, imported from the American continent, one third of its population being devoured by a sort of a putrid fever." From that date on the bonfire of which the yellow flame was kindled in the West-Indian Archipelago, and the mass of new European visitors made the fire

inextinguishable. In the years 1653, 1667 and 1668 Cuba was attacked again and this condition lasted until Gorgas applied the principles of Finlay early in 1901.

Barbados suffered an attack in 1647 for the first time, and in 1695 Admiral Wheeler's fleet was destroyed before he could attack Martinique. In 1697 Admiral Neville suffered similarly.

Santa Lucia was visited in 1664. There, 1,411 soldiers were killed out of a garrison of 1,500 men. In 1690, Martinique suffered one of the most fatal epidemics, known as Oriflamme, this being the name of the ship which brought it. As this ship came from Siam, making a call in Brazil, the disease was called the "Siamese Illness."

According to Rocha Lima, the first appearance of yellow fever in South America took place in 1658, in Pernambuco; it appeared in New York in 1668, in Boston in 1691, in Philadelphia in 1669 and in Charleston in 1699. It cannot be doubted that by the end of the century yellow fever was the owner of the American soil, and that outbreaks recurred each time a European expedition tried to penetrate into the West-Indian ring. Perhaps the Caribs played an important role in keeping this fire alive, by their numerous warring expeditions to the different islands.

However, from the 18th century on, because of the great military expeditions and the facilities in the passenger routes, intensive yellow fever epidemics broke out. According to Griffith Hughes' "HISTORY OF BARBADOS," the name yellow fever originated in that island. The English speaking countries adopted that name, while the Spanish speaking ones called it "Black Vomit," after the paper by the Spanish physician Juan Jose Castelbondo, a resident in Cartagena of Indias, which was published in 1729.

In the 18th century Havana was brutally attacked several times, but we will mention only the epidemic of 1762, when the victorious army of the Earl of Albemarle saw his triumphant capture of Havana blurred by the havoc played in his ranks by yellow fever. Out of his 15,000 men only 7,000 came out alive. The seven Spanish regiments which arrived in Cuba in 1780, for the purpose of strengthening the forces of General Bernardo Galvez in Louisiana, were swept away and the same happened to the fleet of General Aristizabal when it returned from Santo Domingo.

Admiral Graydon in Guadeloupe in 1703, and Admiral Vernon facing Cartagena in 1741, experienced the power of yellow fever. The latter, who had sailed from Southampton with 27,000 men to conquer Mexico and Peru, lost 20,000 men in his ill-fated enterprise. Gray's army in Martinique, and another one commanded by Abercrombie intended for the conquest of the other small islands, saw their 13,000 men dwindle under the impact of yellow fever.

Santo Domingo was a permanent focus during the whole century, and there were times when yellow fever was so intense in the Greater and Lesser Antilles, that it is hard to say who was the infected and who the infector.

If we move to the African Continent we find records of an invasion in Senegal in 1740, and in Sierra Leone in 1764.

Spain paid a high price for its trading monopoly because Malaga suffered five epidemics, causing the death of more than 3,000 human beings in 1741. Cadiz was scourged several times, and the Canary Islands suffered their first severe attack in 1771.

First the cities of the British Colonies in North America, and later on those of the United States, were attacked on several occasions, making life practically impossible in some of the ports on the Atlantic coast and on the Gulf of Mexico. New York underwent no less than seven important epidemics from 1702 to 1800. Philadelphia was scourged on eleven occasions and we all know about the 1793 epidemic, so well described by Mathew Carey in his excellent exposition of the horrors suffered by the inhabitants of that city. On this occasion I wish to say a few words of remembrance of the 4,041 persons who died from August to November of that year, and to do homage to our colleagues Hutchinson, Morris, Linn, Pennington, Dodds, Johnson, Glentworth, Phile, Graham and Green, who were the victims of yellow fever while fulfilling the sacred duties of our profession to their very last minutes—here in Philadelphia they wrote a page full of heroism and sacrifice.

Charleston was attacked twelve times and New Orleans suffered impacts on several occasions. The New York 1798 epidemic killed 2,300 persons, in New Orleans 4,044 human beings were lost, and Philadelphia was similarly shaken by the death of 3,446 of its citizens. But this scourge reached other cities, such as Baltimore, Mobile, Norfolk, leaving death and desolation in its path.

In the 19th century, the devastating epidemic took hold among the men sent by Bonaparte to reconquer Santo Domingo. This expedition, 25,000 men strong, under the command of General Leclerc, was totally wiped out by Black Vomit.

Cuba suffered the sternness of this disease in more than twenty-five outbreaks in the period from 1800 to 1887, and we may point out that the Spanish Government lost more than 100,000 men in the two Cuban wars. Unquestionably, yellow fever was the best ally of my country.

In this century, the American cities along the Gulf of Mexico were the ones mainly visited. New Orleans had epidemic outbreaks from 1800 to 1878, and in one year alone, in 1853, 8,101 out of 29,020 patients died. Mobile, Houston, Galveston, Pensacola, Key West, etc., were attacked. We will not mention the total number of visits suffered by New York, New Jersey, Boston,

Savannah, Norfolk, where in 1855 yellow fever killed 2,000 persons. Charleston had five big outbreaks, of which the one in 1866 took 4,565 lives. In Memphis, Tennessee, scourged no less than five times, the epidemic killed 5,150 citizens in 1879 out of a total of 17,600 cases.

If we cast a rapid glance over the Old Continent, we find Madrid shaken in 1878, and the epidemics recorded in that century in the cities of Cadiz, Cartagena, Jerez de la Frontera, Malaga and Barcelona were indeed horrible, as in Cadiz alone, a city which had 57,000 inhabitants at the time, 48,000 cases of yellow fever were recorded, with 7,307 deaths. Jerez de la Frontera had more than 14,000 deaths and its population was practically desolated. In 1821, Barcelona lost 20,000 lives and Cartagena, in 1804, some 12,000 of its citizens. Through the Canary Islands, it passed triumphantly on three occasions, leaving behind a wake of mourning and pain.

In 1856, Lisbon lost approximately 18,000 human beings and Livorno, Brest, Marseille and Saint Nazaire were invaded. It reached Gibraltar and Southampton. Dr. Graves left a great description of the havoc it played in Dublin in 1826.

In Africa the main epidemics took place in Senegal and Sierra Leone.

This brief historic outline of yellow fever epidemics brings us to the year 1878, when the disease invaded more than 100 cities and villages in the United States, mainly in the States of Louisiana, Mississippi and Tennessee. The number of cases reached the figure of 120,000 out of which 20,000 were lost. Besides taking a terrible toll in human life, it caused the country the economic loss of 100,000,000 dollars.

In view of this enormous destruction, the Congress of the United States passed a law in March 1879, setting up the National Board of Sanitation, appropriating the amount of $50,000.00 for it. This amount was increased to $500,000.00 on July 2nd. The first resolution passed by the Board was to organize a Commission to visit the West Indies, with the object of studying Black Vomit in the supposed source areas of the disease, with a three-month stay in Havana and then to carry on its work in Rio and other endemic areas. This Commission which I call the FIRST AMERICAN COMMISSION FOR THE STUDY OF YELLOW FEVER IN CUBA, was formed by Doctors Stanford E. Chaille, who presided over it, George Miller Sternberg, Secretary, Juan Guiteras, Engineer, Mr. Thomas Hardee, and Messrs. Rudolph Matas and Henry Marcel. (We are fortunate to have today in New Orleans that great figure Matas, the only survivor of that Commission.)

The report of this Commission was rendered on November 16th, 1879, and among its conclusions the main one reads: "Yellow fever is an epidemic, transmissible disease and the agent capable of transmitting the disease must be in the air." This conclusion, plus the microscopic preparations he had

obtained, led Dr. Carlos J. Finlay—who had participated in the work of the Commission—to think of the possibility that the causative agent should be looked for in the blood vessels. Thus, Dr. Finlay moved along a new route, giving up his ideas in connection with atmospheric alkalinity, which he had studied up to then. All the foregoing, the "Nest Theory" held at the time by Bemis, Stone et al., as well as the study of the evolutionary cycle of certain fungi, strengthened him in his new belief. He expressed himself at the International Sanitation Conference, held in Washington on February 18th, 1881, as to the three conditions necessary for the propagation of yellow fever, namely:

1. The existence of a previous case of yellow fever.
2. The presence of a subject capable of acquiring the disease.
3. The presence of an agent, independent of the disease as well as of the patient, but necessary for the transmission of the same.

The echo is still alive of the revolutionary ideas contained in Dr. Finlay's paper titled "The Mosquito Hypothetically Considered as the Agent in the Transmission of Yellow Fever," read by him in the Academy of Medico-Physical and Natural Sciences of Havana, in its session on August 14th, 1881. In this paper, the third Washington conclusion carries name and surname, as he further points to the Culex mosquito, known today as the *Aëdes aegypti*.

How was it to be believed what seemed a heresy? How could Finlay present a thesis introducing the intervention of a new element, insects, in the transmission of the disease to a healthy person? Being ahead of his time, it is natural that he was not understood. He remained so for over more than twenty years. Let us review what the status of yellow fever was at the time, in order to understand the greatness of his work.

What was it that explained this rapidly changing manner of attack? We are not going to discuss the diversity of etiologic conceptions which were uttered, full of vagueness and lacking scientific basis, but which were the object of bitter disputes among its originators, although these conceptions kept everything concerning yellow fever in a deep mystery.

The work of Pasteur opened a new field for the etiology of yellow fever, and germs and bacteria were described.

In view of the great diversity of bacteriologic opinions, the President of the United States, Grover Cleveland, issued an order dated April 29th, 1887, appointing Dr. George M. Sternberg, U.S. Army Surgeon, to go to Rio de Janeiro and Mexico to study matters connected with these diverse opinions. The findings were read by Sternberg before the College of Physicians of Philadelphia in April, 1888, and published in the Medical News of April 28th of the same year. It was evident that he had not found anything of importance in research on yellow fever.

In the meantime, Dr. Finlay continued his tenacious work to prove his genial hypothesis, effectively assisted by the only man in Cuba who believed him, his inseparable companion Dr. Claudio Delgado, encouraged in his irrevocable faith by his teacher Weir Mitchell, one of your own sons, and backed by Rudolph Matas in the beautiful city of New Orleans.

Upon his return to the United States, Dr. Sternberg, an untiring man, asked to be sent to Cuba to continue his research. His request was granted by Special Order No. 93, of April 21st, 1888, issued by the Secretary of War, William C. Endicott. This is what I call the SECOND AMERICAN COMMISSION FOR THE STUDY OF YELLOW FEVER SENT TO CUBA. Because its means were limited and a report had to be submitted to the President before June 20th, he returned to the United States. This made it possible for him to go to Decatur, Alabama, to study yellow fever in the South of the United States.

Set on solving the enigma of the disease, he asked to be sent to Havana again, and his request was granted by Order No. 30, issued by the War Department in Washington on February 4th, 1889. His tenacious and persevering work succeeded in eliminating many germs claimed to be the cause of Black Vomit.

Sternberg came to Cuba as the Secretary of the Chaille Commission, and in his eagerness to solve the riddle, he visited us later on, on two occasions. Sternberg was an experienced bacteriologist and he used the standard methods of bacteriology in finding the solution. He did not heed the counsel of Finlay, although on many occasions they had discussed man's impotency to defeat the terrible disease. Possibly no one had greater opportunity to apply Finlay's principles and thus solve the riddle than Sternberg. He had an additional occasion, when he visited Mexico, and made the acquaintance of Dr. Daniel Ruiz in Vera Cruz, who, in 1885, had inoculated blood of a yellow fever patient into a healthy person to determine whether thereby the infection could be transmitted. According to Sternberg's report: "At the time of my visit to Vera Cruz he expressed his complete willingness to repeat these experiments in my presence. This was exactly what I desired, and accordingly Dr. Ruiz made three inoculation experiments upon three unacclimated persons in the hospital."

These inoculations failed and he added: "I was therefore anxious to make other experiments before leaving Vera Cruz but the time fixed by my orders expired without my having had an opportunity to do so." Thus we see on that occasion that the time factor possibly prevented Sternberg from achieving what Welch was to recommend later to the Reed Commission.

What we have quoted above is contained on page 109 of the book by Martha Sternberg titled "GEORGE M. STERNBERG, A BIOGRAPHY." The lines quoted are preceded by the following words: "Dr. Finlay of Havana

believes that the disease is commonly transmitted by mosquitoes, which, after filling themselves from a yellow fever patient, transmit the germ by inoculation into susceptible persons."

It is really unexplainable why Sternberg, a man of proved medical culture, did not follow the ideas of Finlay, especially when he had failed to make any progress following his own ideas.

Let us now mention that Dr. Guisseppe Sanarelli in 1887 published a paper in the Annals of the Pasteur Institute, claiming that the cause of yellow fever was the icteroid bacillus, discovered by him. The publicity given to this organism was such that the Surgeon General of the United States Army, General Wyman, at the end of 1898 sent a commision to Cuba, made up by Doctors Wasding and Geddings, of the hospital service of the Navy, to verify the claim. This is the commission which I call the THIRD AMERICAN COMMISSION FOR THE STUDY OF YELLOW FEVER IN CUBA. Wasding and Geddings found the Sanarelli bacillus in thirteen patients out of the sixteen studied thus continuing the charlatanry prevalent at the time.

Sternberg, who had been promoted to the rank of Surgeon General, did not accept the ideas of Sanarelli, nor was he convinced by the conclusions of Wasding and Geddings. He decided to send Dr. Aristides Agramonte to Cuba with instructions and authorizations to do everything possible to clear up the question. In his paper titled "RELATION OF THE ICTEROID BACILLUS TO YELLOW FEVER," Dr. Agramonte proved that there was no connection between the two.

It will be noticed that at the end of the century, the etiology of yellow fever was still an enigma except for Finlay, and we make an exception in his case because, after he expounded in 1881 his doctrine of the transmission of the disease by mosquitoes, he continued to work untiringly to prove to the world his scientific truth, studying in an exhaustive manner all the phases of it, namely, its etiology as well as bacteriology, epidemiology, clinical symptomatology, pathologic anatomy, prophylaxis, and describing minutely the anatomy of the *Aëdes aegypti,* its habits and customs.

In the first period of Dr. Finlay's professional life connected with yellow fever, comprising the years 1865 to 1881, he wrote ten papers on the subject, and from the last named date to his death, he published eighty papers more related to the Black Vomit. His articles were written in several languages—English, French, German and Spanish, but mostly in English—and in them he shows his deep knowledge. We cannot mention his complete works here, but we believe it would be well to single out, in addition to the paper read by him on August 14th, 1881, in the Academy of Sciences, the paper he made known in that same place in two of its sessions, namely, those of January 31st and February 29th, 1884, titled "EXPERIMENTAL YELLOW FEVER COMPARED WITH THE NATURAL ONE IN ITS MORE BENIGN FORMS."

In the first part of this paper he deals with its incubational period and discusses its diagnosis in benign cases in some of which albuminuria is present, while in others it is not. In the second part he deals with Experimental Yellow Fever, inoculated by mosquito bites, setting down the manner in which to perform the inoculations. He masterly describes the first ones carried out on Spanish soldiers stationed at Cabana Fortress, as well as those performed on Jesuit Fathers in the "San Jose" farm, in Marianao (where in 1900 the Reed Commission was to establish the Lazear Camp), and in his conclusions Finlay says: "From the fact that yellow fever is inoculable by mosquito bites, there follows the need of protecting the patients attacked by that affection from the stings mentioned in order to prevent the propagation of the disease." We find here, specifically pointed out, the fundamental principle in force today in the prophylaxis of yellow fever. In the part devoted to its diagnosis he deals with the so-called "acclimation fever," pointing out the ephemeral attacks of the disease which render immune those suffering from the ailment, a Finlayan concept now known as "INAPPARENT YELLOW FEVER." He also discusses the incomplete or abortive forms of yellow fever, in which the symptomatologic picture may be restricted to a feverish type characteristic of ordinary yellow fever, and its evolution within the limits pointed out, the other elements of the diagnosis being reduced to their slightest expression, or being completely absent.

In his paper read at the Convention of Hygiene and Demography, held in Budapest in September 1894, he emphasized: "To prevent yellow fever the following should be done:

1. Prevent mosquitoes from biting patients with yellow fever.
2. Destroy as many contaminated mosquitoes as possible.
3. To consider a place free from yellow fever, it must be kept in mind that mosquitoes fed on yellow fever patients may live from thirty-five to forty days under favorable conditions; therefore, prevention must last until that period has passed, as a contaminated mosquito is infectious during its lifetime."

Please consider the value of these postulates in the light of our present knowledge, and to what an extent that misunderstood man, who found no respect for his scientific truth, was a prophet.

In his memorable paper titled "REVIEW OF THE PROGRESS ACHIEVED IN THE 19TH CENTURY IN THE STUDY OF THE PROPAGATION OF YELLOW FEVER," published in 1901, he gathered with the help of his great companion, Dr. Claudio Delgado, the data on all experimental inoculations practiced thus far, a wonderful exposition of his tenacity and faith in his convictions. It may be argued that the results were not completely conclusive, but there can be no doubt that he established the

firm basis of a new doctrine, which would make possible the full confirmation of his ideals later on. It is my opinion that if his guiding lines to put an end to yellow fever had been followed, the disease would have been conquered years before, thus saving thousands of human lives.

Before bringing to an end this part of our paper relating to Finlay, it must be mentioned that yellow fever was not his only concern. He worked on cholera, filariasis, goiter, tetanus, ophthalmology, cancer, leprosy, tuberculosis, trichinosis, beriberi, glanders, etc., publishing more than fifty papers on subjects concerning public health other than yellow fever.

I do not want to tarry on the subject of the different opinions held in connection with insects prior to Finlay's nor on the ones which were formulated after that, as the majority of them deserves no special attention. We will limit ourselves to mention Nott and Beauphertuy, quoting from Dr. H. R. Carter's book, "THE PRACTICE OF MEDICINE IN THE TROPICS": "Neither Beauphertuy nor Nott, in spite of the ingenuity of the theories expounded by them, may be considered as predecessors to Finlay regarding the theory of the transmission of yellow fever by mosquitoes." However, I may add that at the Convention on the History of Medicine, recently held in Rome, Italy, this problem was definitely settled.

While Finlay was carrying out all that has been reviewed above, the drama in Cuba went on unfolding itself, was everlastingly present on its horizon. And yet no one paid attention to him—he was still the object of mockery. This gloomy picture led General Sternberg to appoint the Reed Commission, or the FOURTH AMERICAN COMMISSION FOR THE STUDY OF YELLOW FEVER. Thus, there arises Special Order No. 22, of the Headquarters of the Navy in Washington, dated May 24th, 1900. In the new Order we find new proofs of Sternberg's nonacceptance of Finlay's principles, quoting from the book "MEMOIRS OF WALTER REED," by General Albert Truby, who lived through the whole Cuban episode of 1900 (pp. 89 and 90): "Having for years given thought to this subject, I became some time since impressed with the view that in yellow fever, as in malarial fevers, there is an "INTERMEDIATE HOST." I therefore suggested to Dr. Reed, President of the Board, appointed upon my recommendation for the study of this disease to the Island of Cuba, that he should give special attention to the possibility of transmission by some insects, although the experiments of Finlay seemed to show that the insect was not a mosquito of the genus Culex, such as he had used in his inoculation experiments. I also urged that efforts should be made to ascertain definitely whether the disease can be communicated from man to man by blood inoculations." This was published by Sternberg in his paper titled "THE TRANSMISSION OF YELLOW FEVER BY MOSQUITOES," in "Popular Science Monthly" in July 1901. Ten years before, in "The American Journal of Medical Sciences," No. 102, 1891, Sternberg published a paper titled "DR. FINLAY'S MOSQUITO INOCULA-

TIONS," in which he stated that such works were unworthy of consideration, which brought about Dr. Finlay's rejoinder sent to the Editor of the Journal at the time, Dr. E. F. Davis, who was later to be the brilliant professor of obstetrics at the Jefferson Medical College.

The Reed Commission started its work by conclusively eliminating the importance of the Sanarelli bacillus. The four members of the Commission, Reed, Carroll, Lazear and Agramonte, promptly did away with that charlatanry. In view of the negative results of this research, the Commission seemed in the process of engaging itself in the bacteriologic study of the intestinal flora of patients with yellow fever and of healthy persons. However the guiding hand of General Wood, the findings of Dr. Ross in regard to malaria, and the observations of Carter on the extrinsic period of yellow fever, perhaps all these happily led the Commission to follow Finlay's path.

Thus, the Reed Commission started its studies receiving from Dr. Finlay all the data which, according to his opinion, were of interest. Reed was forced to abandon his work in Cuba. He was called to the United States to report on an epidemic of typhoid fever in the army in the South, and he left Cuba on August 2nd, 1900. His departure brought about the following distribution of the remaining members of the Commission: Lazear was to work on the breeding and feeding of mosquitoes; Carroll on bacteriologic studies and Agramonte in Hospital No. 1. At the Board meeting of August 1st, held in Havana and presided over by Reed just before his departure, it was evident that Lazear was the only member who was enthusiastically for the mosquito theory. To prove this last statement we quote part of a letter Lazear wrote to his wife, dated August 23rd, contained in Hench's "DR. JESSE LAZEAR AND HIS CONTRIBUTION TO THE CONQUEST OF YELLOW FEVER": "Reed and Carroll have been at their bacteriologic work for a long time. . . . They are interested in the controversy with Sanarelli. I would rather try to find the germ without bothering about Sanarelli. The malarial work is my own."

Undoubtedly the plan of the Commission comprised experiments with human beings, so Lazear between August 11 and 25 applied infected mosquitoes to nine American soldiers, including himself and Drs. Carroll and Pinto. These experiments failed because the infected mosquitoes were not yet "ripe." On August 27th, Lazear inoculated Dr. Carroll who promptly developed yellow fever and on September 6, Private Dean developed the disease after inoculation also. Two days later Lazear wrote his wife (Sept. 8) the following: "I rather think I am on the track to the real germ, but nothing must be said as yet." According to Agramonte's book "THE INTERNAL HISTORY OF A GREAT MEDICAL DISCOVERY," when Dean took sick with yellow fever and the diagnosis was established by Dr. Roger P. Ames, a cablegram was sent to Dr. Reed reading: "The theory of the transmission of yellow fever by mosquitoes, so much questioned from the beginning and

the far-reaching importance of which we hardly appreciate, has been indubitably confirmed."

Shortly thereafter a lamentable happening took place: Lazear, infected by what appeared to be an experimental sting, died victim of the disease on September 25th, thus ending a life full of promise, the life of a man who, with masterly hands, guided the definitive experiments to confirm what Finlay had said. At that moment another name, JESSE LAZEAR, was offered as a sacrifice to save thousands of lives, and under the blue sky of our country the light of his reasoning was clouded. From our land there flew his last thoughts to his wife and daughters, and to his future boy who was to bear the honor-giving name of Lazear.

Shortly after this loss, on October 3rd, Reed returned to Cuba and immediately thereafter, using the data tenaciously worked out by Lazear, he presented at the meeting of the American Public Health Association, held in Indianapolis on October 23rd, the paper "ETIOLOGY OF YELLOW FEVER. A PRELIMINARY NOTE," in which he called the attention of the scientific world to the fact that what had been held by Finlay since the year 1881 was a truth.

Walter Reed returned to Cuba in the first days of November and together with General Leonard Wood, planned the construction of a Camp in which to carry out the experiments which Lazear had already outlined, in order to prove conclusively the mosquito theory. He selected as its location the "San Jose" farm, in Marianao, where in 1883 Finlay had performed experimental inoculations upon Jesuit Fathers. We are of the opinion that Reed selected that place following Agramonte's suggestion, who knew that in spite of the yellow fever epidemics in Marianao, there were no cases of the disease on the farm, surely because the *Aëdes aegypti* were not present. The Camp was named after Lazear, in honor of the hero.

Two cabins of identical measurements were built, and in one of them, bearing the number 2, experiments with infected mosquitoes were made on volunteers, while in the other, bearing the number 1, it was proved that the FOMITES had nothing to do with the transmission of the disease.

This group of volunteers—made up of Americans, Spaniards and Irishmen—showed to the world their greatness and courage in experiments carried out in a disciplined manner, and with sufficient resources. The results confirmed the greatest scientific truth, a truth our glorious Carlos J. Finlay had offered and the medical world had refused to accept.

In 1940, that spot of Cuban land which Hench correctly identified as Cabin No. 1 with the help of Moran, one of the great volunteers, was still kept as a symbol of that great event. The Cuban Government declared it a National Monument. This was not possible with Cabin No. 2 which had

been destroyed by the hurricane which attacked Havana in 1926. Cabin No. 1 was restored to its original status. A park was constructed around it in which bronze medallions of Finlay, Wood, Lazear, Reed, Agramonte, Carroll and Delgado were placed, with two bronze plates bearing the names of all those who volunteered and of the persons who contributed to the definitive conquest of yellow fever.

Shortly after the holding of the Third Pan-American Medical Congress in Havana in 1901, Reed presented the conclusions of the Commission, which permitted Gorgas (another unbeliever of the Finlay theory) to carry out the great work of making Havana wholesome which started on the 4th of February, 1901. We may call this the first brilliant work in Public Health, irrefutably demonstrating its results. In February, five deaths were recorded in Havana, one in March, none in April, May and June, one in July, two in August and two in September. What had been the brutal and ferocious scourge of its inhabitants over four centuries, finally disappeared. Indubitably, the definitive conquest of yellow fever alone justifies the Spanish American War, in spite of the fact that in the period between 1898 and 1900 the United States suffered 231 deaths of yellow fever out of total of 1,575 cases.

After his success in Havana, Gorgas, supported by the Governor of the Isthmus of Panama, General G. W. Davis, made possible the construction of the Canal which Lesseps was not able to build years before. To accomplish this he simply had to put into practice a campaign against the *Aëdes aegypti*, which was the key to his great success. There can be no doubt that the disappearance of yellow fever in Panama, and his victorious campaign against malaria, are eloquent facts revealing Gorgas' scientific, sanitarian, diplomatic and moral qualities, as well as his organizing and executive abilities, which place him on the level of the first sanitarian of the world.

Now, let my final words express to the Jefferson Medical College, our joy and profound happiness for taking the initiative in honoring Dr. Carlos Finlay on the Centennial of his graduation.

Like a loving mother, this honorable institution molded the majestic figure of Dr. Finlay and today I feel and all of you must sense, his gigantic figure being projected all around us. To you, Jefferson Medical College, the esteem of my country and our profession must be shown for honoring one, who loved and honored you during all his professional life and for maintaining after 100 years a faith and confidence in his greatness as did his teacher, Dr. Weir Mitchell, while Finlay struggled to prove to a doubting world his great scientific truth.

I thank you.

PROGRESS IN THE CONQUEST OF YELLOW FEVER DURING THE PERIOD 1905-1930

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The remarkable discovery by Reed and his colleagues, at the turn of the present century, that yellow fever is an insect-borne disease, was the first, and the most outstanding, landmark in the long struggle against this dreadful disease. The conclusion of these workers that the agent solely responsible for the transmission of the infection from person to person was the mosquito, *Aëdes (Stegomyia) aegypti,* (L), pointed clearly to the eradication of this insect as the most practical method of eliminating the disease. Sanitarians were quick to accept this principle and put it into practice, and, at the beginning of the period we now have under consideration, successful control campaigns have been completed, or were in progress, in Havana, Veracruz, the Isthmus of Panama, and Rio de Janeiro.

During the next twenty years many successful campaigns were waged against yellow fever, and it is not surprising to find, at an early date, that some of those responsible for planning and directing the work began to foresee the time when the disease would entirely disappear from the Americas. The epidemiological concept upon which the control measures were based was a very simple one. Nevertheless, the experts of the time were satisfied that it took into account all the factors concerned, and it was not until after the lapse of another quarter of a century that its short-comings were brought to light. The concept was based on the belief that man was the only susceptible vertebrate host, and that the mosquito, *Aëdes aegypti,* was the sole vector. The mosquito became infected by feeding on a yellow fever patient during the first three or four days of the illness. Then after an incubation period, the length of which varies with the temperature, the mosquito becomes infective and continues so for the remainder of its life. In this simple man-mosquito-man cycle it is obvious that, for transmission of the disease to continue, there must be an ample supply of the insect vector as well as an adequate number of susceptible individuals. If either of these factors fails, transmission will cease and the outbreak will come to an end. The simplest way in which to bring this about was by attacking the vector. It is a domestic mosquito which

breeds, for the most part, in artificial water containers in and around houses. Breeding can readily be controlled by weekly inspection of these containers, with destruction of larvae when they are found.

It was observed, early in the campaign, that *aegypti* control, in many cities in Central and South America, rapidly led to the disappearance of the disease. Furthermore, it was found that successful control in the large centers was usually accompanied by the suppression of the infection in the surrounding countryside. From this it was concluded that yellow fever could persist only in large cities, where there was an adequate influx of susceptible strangers and new-born children to prevent the disease from burning itself out through failure of the human host. If the vector was controlled in these large cities, or key-centers as they were called, yellow fever should disappear from the community, since outbreaks in all the smaller places were deemed to be secondary, and unable to persist in the absence of the main focus.

Following the original anti-mosquito campaign in Havana, successful control measures were carried out in many places which had been notorious danger spots in subtropical and tropical America. An epidemic in New Orleans in 1905 was quickly brought under control and the United States was not again invaded. Yellow fever gradually vanished from the West Indies, and a successful control campaign was begun in the Amazon basin in 1912. In 1916, the Rockefeller Foundation, which had become actively interested in yellow fever, appointed a commission to make a survey of the situation in South America. In their report they concluded that the only endemic center in South America was in Guayaquil, Ecuador. They recommended that the infection be eliminated from Guayaquil, that the east coast of Brazil and the southern littoral of the Caribbean be kept under observation and that investigations be extended to Mexico and West Africa, both of which regions were under suspicion. They were satisfied that the program should have as its ultimate objective the complete extinction of the disease.

The advent of World War I delayed the initiation of the campaign in Guayaquil, and it was not until 1918 that it again came under consideration. At this time it was deemed advisable to learn more about the disease in Ecuador, and a special commission was appointed to undertake this. Its members included experts in clinical medicine, epidemiology, bacteriology, and chemistry, and they arrived in Guayaquil in July, 1918. A few months later came the startling announcement by Noguchi, the commission bacteriologist, that he had isolated, from patients said to be suffering from yellow fever, a leptospira, which when injected into guinea pigs, produced lesions suggestive of yellow fever. Later, this same organism was isolated by Noguchi, and by other investigators, during yellow fever epidemics in Mexico, Peru and Brazil. In due course, and after much experimental study, Noguchi concluded that this was the causative organism of yellow fever, and he named it *Leptospira icteroides.* Although this conclusion was later proved to be erroneous, it was

soon almost, but not quite, universally accepted. Although the findings of Reed and his associates had been amply confirmed by many workers in many countries, they were overlooked when this new and contradictory evidence was brought forth by a distinguished scientist. The result was to further confuse the issue where the etiology of yellow fever was concerned. Presumably the explanation of the error lies in the fact that, clinically, yellow fever and spirochetal jaundice may closely resemble one another and, in addition, the two diseases are sometimes present at the same time. Undoubtedly, Noguchi isolated the etiological agent of the disease with which he was working, but, unfortunately, that disease was not yellow fever. The episode illustrates very well the ease with which, under certain circumstances, a false scientific deduction may gain general acceptance and be treated as fact until, at some future date, some one reinvestigates and discovers the error. On the other hand the experience of Carlos Finlay illustrates equally well the difficulties which may have to be overcome in getting recognition for a conclusion which is eventually proven to the satisfaction of everyone to have been valid.

In 1918, the Rockefeller Foundation, in collaboration with the Governments of the countries where yellow fever might be found, launched a full-scale campaign for the eradication of the disease from the Western Hemisphere. The first project, which was commenced in Guayaquil, late in 1918, was a conspicuous success, and the city was declared free of the disease in 1920. During the next five years a long series of successful campaigns was carried out in many countries in Central and South America, and, by 1925, it was believed that the only remaining foci of yellow fever in the Western Hemisphere were in a relatively small area of Northeast Brazil. Control measures which were in progress in this area had already yielded promising results. Thus, in a comparatively short space of time success had been achieved, or so it was believed, and yellow fever was about to disappear from the Americas. Optimism reached a new peak and preliminary arrangements were made to tackle the problem in Africa. Unfortunately the events of the next few years brought keen disappointment to those who had convinced themselves that the struggle against yellow fever in the Western Hemisphere was over.

In 1926, there was a sharp increase in the number of cases in several states in Brazil. These were quickly brought under control and a satisfactory explanation was found for their occurrence. However, a more serious setback occurred in 1928, when the disease appeared in epidemic form in Rio de Janeiro for the first time in 20 years. As this city was almost one thousand miles from the known infected area, no satisfactory explanation could be made at the time as to how the disease had been introduced. Following this, cases appeared in numerous places over a wide area in Brazil, and a small epidemic was reported from the interior of Colombia. In the light of these events it gradually came to be realized that there was something wrong and, perhaps, the epidemiology of yellow fever was not quite as simple as had been supposed. The skill and diligence with which this new problem was tackled and

solved is a most interesting feature of the period immediately following that covered in this review.

Let us now direct our attention towards Africa. Although it is now believed that yellow fever may possibly have originated in Africa, it is not known when the disease first made its appearance there. The available information suggests that it was not recognized as a definite entity until late in the eighteenth century, but it seems reasonable to assume that it must have existed much earlier than that. It is known, however, that, since 1778, it has been almost continuously present upon the West Coast of Africa, and there have been few years since that date when the records have failed to comment upon it. During these early times it was believed to be confined to a comparatively narrow strip along the West Coast, which extended from Senegal in the north to the Cameroons in the South. It sometimes invaded short distances into the interior, along certain much-travelled lines of communication, but its presence farther inland in West Africa, or in Central or East Africa, was never detected, or even suspected. Furthermore, it was rarely diagnosed in the African, and it was only when non-Africans, usually called "Europeans," were attacked, with the attendant high mortality, that the alarm was raised and the event made a matter of record. Early expeditions brought back alarming reports of the deadly fever of the coast, which was referred to as "yellow-jack," "Lagos fever," "fever of the Bight of Benin," and other terms usually referable to the district in which it was encountered. It was these reports which were, in large measure, responsible for the West African Coast becoming known as the "white man's grave," an unsavory reputation which it has never entirely lost.

Interest in the yellow fever problem in Africa was renewed and heightened when it became known that it was an insect-borne disease, and during the next twenty-five years repeated commissions were sent to the West Coast to study the situation and report upon it.

In 1910, Sir Rupert Boyce, whose experience in the New Orleans epidemic in 1905, and subsequently in British Honduras and in the West Indies, fitted him to carry out intensive studies of this disease, spent considerable time upon the West Coast. He collected data upon the recurrence of yellow fever in each of the colonies scattered along the coast, and he presented irrefutable evidence that, for more than one hundred years, the coast had never been free from infection. However, there were still those, at home and abroad, who denied the existence of yellow fever in Africa, claiming that the diagnosis had been confused with other tropical diseases. We know now, of course, that this mistaken conception was, at least in part, due to the fact that the disease was much more prevalent than was supposed in the African population, and that this was the source of the sudden and unexplained outbreaks which occurred, from time to time, among the highly susceptible, but very small white population. The disease was rarely recognized in the African

because the great majority of such cases was so mild as to render diagnosis difficult or impossible, and because febrile illness among Africans was rarely brought to the attention of the relatively very few individuals who were competent to make a diagnosis.

The publication of the reports by Boyce led to considerable agitation and much controversy, and, in 1913, the British Government appointed a yellow fever commission to investigate and report on the situation in West Africa. The members of this Commission spent three years in collecting data. They devoted little time to personally investigating the disease, and concerned themselves mainly in reviewing the evidence of others, who had reported the presence of the infection in Africa. In their report they expressed the view that yellow fever had long been present in West Africa, and that it was widely distributed. In 1910 and 1911, it was prevalent over a wide area, and there were epidemics in Freetown, Bathurst, Sekondi, Accra, and elsewhere. In 1913, there were outbreaks in Lagos, Accra, and several smaller places. The alternation of periods of widespread epidemic conditions, with intervals of relative quiescence, so characteristic of yellow fever, was a conspicuous feature of the picture in West Africa. It was during one of these quiescent periods that a Commission was sent to West Africa, in 1920, by the Rockefeller Foundation, to study the problem. No authentic cases were seen, and the Commission was unable to decide whether the African disease, diagnosed as yellow fever, was actually yellow fever, and, if so, whether control measures would be feasible. It was recommended that the report be treated merely as a progress report, and that another Commission be appointed to carry out a more extensive and prolonged study in West Africa.

Accordingly, in 1925, still another Commission was sent to Africa by the Rockefeller Foundation. This group, known as the West African Yellow Fever Commission, was fully equipped to undertake a thorough and comprehensive study. Its primary objective was to determine whether yellow fever in Africa was identical with that seen in South America. Then, as the program developed, it hoped to isolate the causative organism of the African disease, to discover the mode of transmission, and to identify the areas in which it was endemic.

Field studies were commenced late in 1925, and, in the absence of reported cases, an intensive search for the disease in the African population was undertaken in Nigeria and on the Gold Coast. These efforts were successful, in 1926, when an epidemic was discovered in Asamankese, Gold Coast, a town of approximately 5000, situated in the cocoa-belt fifty miles northwest of Accra. It is of interest to note that this was the first large outbreak, exclusively in the native population, ever observed in West Africa. Although the epidemic was on the wane when the study was initiated some fifty cases were seen in which a clinical diagnosis of yellow fever seemed justified. In addition, a large number of persons were observed who were suffering from a mild febrile ill-

ness in which a clinical diagnosis could not be made. Of the fifty cases included in the study, eight were fatal, eleven were classified as severe, and the remainder were placed in the categories of moderately severe and mild. Later in 1926, and during the early months of 1927, similar, though somewhat smaller, epidemics were studied in two other towns on the Gold Coast and an additional sixty cases were added to the total included in the investigation.

These epidemics afforded an excellent opportunity to study the clinical and pathological features of the disease as it occurred in the African. They left no doubt in the minds of the investigators that fatal and severe yellow fever *did* occur in the African, although the impression was gained that the mortality was very much lower than had been reported in epidemics involving Europeans. Furthermore, the evidence indicated that, clinically and pathologically, the disease was the same as that seen in South America. However, repeated attempts to isolate the *Leptospira icteroides,* or any other organism, failed. Blood specimens taken from over sixty cases during the early days of the illness were inoculated into large numbers of guinea-pigs and into larger numbers of tubes of the special medium recommended by Noguchi for the culture of the *L. icteroides.* The results were completely negative. As this evidence accumulated it became more and more evident that *L. icteroides* was not the causative agent of African yellow fever, and that progress in the laboratory could not be expected until a suitable experimental animal was found. The search for a susceptible animal became the problem of prime importance, and included in the numerous species selected for trial was the rhesus monkey.

A shipment of these animals arrived in Accra at about the same time that attention was attracted to a small Gold Coast village, called Kpeve, where two Europeans had suffered mild attacks of an illness clinically resembling yellow fever. An investigation in Kpeve indicated the recent presence of suspect cases, and, on June 30, 1927, a blood specimen was secured from one such case. The patient, whose name was Asibi, was an African laborer aged about 28, and the specimen was taken some thirty-three hours after the onset of the illness. It was taken immediately to the laboratory in Accra and inoculated into a rhesus monkey. The animal developed fever four days later on July 4, and was found moribund and in collapse the following morning. Postmortem examination revealed lesions similar to those seen in human yellow fever. Blood and tissue preparations from this animal were inoculated into other rhesus monkeys and the propagation of the now famous Asibi strain of yellow fever virus began with this experiment.

Although the Asibi strain of virus is, perhaps, the most virulent for rhesus monkeys which has ever been isolated, it is interesting to observe that it had its origin in an exceedingly mild human case. When the donor, Asibi, was first seen, on the evening of June 29th, he stated that the illness had commenced suddenly at 3 a.m. that day. His temperature was 103°F., pulse 96, and he complained of very severe headache and pain in the lower back. He

appeared very ill and prostration was marked. When seen the following morning the temperature was down to 99.9°F., the headache, though still present, was much less severe, and his general appearance was much improved. He made a rapid recovery and returned to work a few days later. This was a case in which the onset, as well as the very early signs and symptoms, was characteristic of classical yellow fever in severe form, but, within a few hours, the patient's natural resistance asserted itself to overcome the infection, and the attack rapidly subsided. However, the Asibi strain of virus, soon after its isolation, was responsible for an accidental infection in one of the scientists engaged on its study in the laboratory, and it produced, in him, a fulminating attack with death in ninety-six hours. We have, in this experience, a clear and adequate explanation of the sudden outbreaks in Europeans, which apparently came from nowhere, and whose obscure origin caused much confusion in the minds of early observers in West Africa.

The problem of a susceptible experimental animal had now been satisfactorily solved, and a new and fruitful era in yellow fever research was opened. This important advance, at a time when the gravity of the yellow fever situation was being more and more appreciated, acted as a stimulus, and research was soon going on in many laboratories in Europe and America, in addition to those in Lagos and Dakar, in West Africa. All these studies resulted in a wealth of new knowledge much of which was directly applicable to the solution of the problems encountered by the observers in the field. It should be mentioned, however, that nothing was discovered which in any way disturbed the fundamental facts established by the Army Commission in Havana, in 1900. That remarkable contribution, by Walter Reed and his collaborators, has stood the test of time, and it will always remain as an outstanding achievement in the annals of scientific research.

The great variety of investigations which was carried out in many places following the discovery of a suitable experimental animal resulted in a mass of new information covering almost all aspects of the yellow fever problem. We will confine ourselves here to some of the more important early results which were of particular interest to the epidemiologist. Since there are, in West Africa, numerous species of the genus *Aëdes,* which resemble *aegypti* very closely in their binomics, it seemed logical to determine whether any of these could transmit yellow fever from one animal host to another in the laboratory. In the first series of experiments, undertaken to settle this point, successful transmission resulted with two species of *Aëdes,* other than *aegypti,* and with one other species of an entirely different genus. Work along these lines was continued both in Africa and in South America, with the result that an ever increasing number of species of mosquitoes was incriminated in both countries. These were, of course, as yet only potential vectors, and the part they played in the epidemiology of yellow fever remained to be determined.

While the search for a susceptible animal was in progress, in 1926 and early in 1927, numerous African monkeys of several different species were inoculated with blood from yellow fever patients. The results were persistently negative; no rise in temperature or other manifestations of the disease followed the inoculations. With the finding of the highly susceptible rhesus monkey this work was discontinued for a time, but it was later resumed with interesting results. In the initial study in this series, attempts were made to infect African monkeys of four different species with yellow fever, both by injection of virulent blood from infected rhesus monkeys, and by the bite of infected *A. aegypti.* None of the animals died or showed signs of illness, but, for a number of days, the virus persisted in the blood of monkeys of three different species, and it could be recovered by injecting their blood into susceptible rhesus. Furthermore, it was found that, in the case of at least two species, the virus could be transmitted from African to rhesus monkeys by *A. aegypti* mosquitoes. Finally, it was shown that, following exposure to yellow fever virus, several species of African monkeys developed specific protective antibodies in their blood, although these were not present before inoculation. This work was continued in Africa and similar studies were made in South America. The result was that a considerable number of species of indigenous monkeys in both countries were found to be susceptible to yellow fever virus, in the sense that they could harbor the virus for several days during which time they were capable of infecting possible insect vectors which fed upon them.

When it became known that vertebrates other than man were susceptible to yellow fever virus, and that mosquitoes other than *Aëdes aegypti* could act as vectors of the infection, the question arose whether the epidemiology of the disease might not be more complex than had been supposed up to this time. In any case, this was the first inkling that there might be factors concerned which had not previously been taken into account.

Another important early development in the laboratory was the elaboration of a highly specific test, known as the protection test, whereby it was possible to demonstrate the life-long immunity possessed by the individual who had recovered from an attack of yellow fever. The blood serum of such a person contains specific neutralizing antibodies, and when it is injected into a rhesus monkey along with virulent virus, the animal is protected and remains well. When a normal serum is used which contains no protective substances, the virus is not neutralized and the animal succumbs to the infection.

The protection test was used in West Africa to gain information on the distribution of the disease. This was necessary since it was soon realized that reported cases of yellow fever in Africa gave no indication of the actual incidence of the disease. The great majority of cases in Africans are never seen or recognized, and, consequently, there was no accurate information on the number of cases which had occurred, or on the extent of the area involved.

Blood samples were collected in various communities and injected into rhesus monkeys along with virulent yellow fever virus. The survival or death of the animal determined whether the serum possessed specific antibodies. If the animal survived, the result was taken to indicate that the donor had suffered an attack of yellow fever at some time during his life. The first survey of this nature was concerned with the examination of 240 sera collected from both children and adults in several of the larger cities in Nigeria. The most striking result was the demonstration of the heavy past incidence of yellow fever as compared with reported cases throughout the area; a result which was amply confirmed when more extensive work along these lines became possible. The early surveys were necessarily limited in extent because the only experimental animal available at that time was expensive and difficult to get in adequate numbers. However, this difficulty was overcome, a few years later, when it was discovered that the monkey could be replaced by the white mouse as the laboratory animal. The immunity survey was then extended to practically all parts of Africa.

In this brief review an effort has been made to outline some of the more important events in the history of yellow fever which occurred during the quarter century following 1905. Special emphasis has been placed on results which seemed of most interest to the epidemiologist, and to those responsible for the control of the disease. For obvious reasons, it has not been possible, at this time, to discuss a host of investigations on other aspects of the problem, many of which yielded significant results. It is hoped, however, that what has been presented will serve to illustrate the great progress made during this era in the long struggle against yellow fever.

JUNGLE YELLOW FEVER

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Jungle yellow fever is the disease in man resulting from the forest cycle of the virus for which the presence of man is not essential. Basically, one is concerned only with the human manifestations, but since it is the epidemiological mechanism rather than the clinical aspect that is distinctive, the discussion here will deal with the characteristics of the virus cycle rather than the clinical picture.

The term "Jungle Yellow Fever" may be blamed on Dr. Fred Soper or on Dr. Jorge Boshell Manrique or on both together. Dr. Soper used it in discussing Dr. Boshell's work at a conference in Bogotá in 1935. Since then many persons have objected to it for numerous and good reasons but nobody has produced a more satisfactory term. The word "jungle" suggests a tropical rain forest to most of us without specifying the location or the composition of the flora and fauna. And yet, notwithstanding its great variation, we at once recognize such a forest as being quite different from any in the northern regions.

Jungle yellow fever is associated with such tropical forests and the virus cycle may assume as many different variations as do the forests themselves; but withal there is a certain consistency and harmony among all of these situations. One may speak of an epidemiological (despite the etymological objections which may be raised, I prefer to extend the term "epidemic" to the forest animal community, including man, rather than to introduce the clumsy word "epizoötic") pattern which holds good generally but the elements of this pattern may differ substantially from one geographic region to another and within the same area at different periods of time.

The first definite association of yellow fever with the forest of which I have knowledge was by Roberto Franco and his associates as a result of their studies at Muzo, Colombia, in 1907 and 1908. They clearly differentiated malaria, relapsing fever and yellow fever; and they attributed the infection to the attacks by silvan mosquitoes on individuals who had penetrated the forest remote from the town. As is not infrequent in scientific matters, Dr.

Franco had outstepped the pace of history and it was not until nearly a quarter of a century later that the accuracy and significance of his observations became generally apparent.

On the basis of Thomas' work at Manáos in 1905, Sir Patrick Manson raised the question of the importance of forest animals, especially monkeys, in yellow fever. He suggested that if the virus could be carried by mosquitoes from man to animals, then it also could be carried in the reverse direction.

Balfour, impressed by the evidence that red howler monkeys had been involved in epidemics of yellow fever in Trinidad, suggested to the British Colonial Office that the possibility of monkeys acting as reservoirs of yellow fever virus would justify a careful study of the monkeys of West Africa. The onset of World War I prevented this plan from being put into operation and many years were to pass before any adequate studies were undertaken. Fundamentally, until the virus was available in a laboratory animal, little definitive work in this area was possible.

The intervening years saw spectacular success in the control and eradication of yellow fever in many regions based on the man-*Aëdes aegypti*-man cycle. The great majority of workers were convinced that this abundantly proved mechanism was the only one in existence. It required the rural epidemic of 1932 in Espirito Santo, Brazil, in the absence of *Aëdes aegypti,* to destroy the complacency and to open an exciting new period in our experience with this disease. It is probably true that had it not been for the work of the previous years which had led to unequivocal methods of diagnosis, this outbreak would have passed unrecognized as to its true nature.

Principles and Mechanisms

It is immediately apparent that several basic conditions must coexist if a natural cycle of virus transmission is to be maintained. These are:

1. The animal in question must be susceptible to the virus. When a small quantity of the virus is introduced into the animal, multiplication of the virus must result; that is, a true infection must occur.

2. Virus in an infected animal must be transferable to other animals, either directly or by mediation of a vector such as an arthropod.

3. In the case of a mediating organism or vector, the circumstances must be such as to permit the transference of virus from the animal to the vector. This is equivalent to stating that host and vector must share the same habitat for at least a portion of the time.

4. The vector must be able to transfer the virus to other susceptible animals of the same or other species with sufficient frequency to permit continuity of the cycle.

Until the present time, in the vast areas of South America and Africa where the virus is maintained endemically without the required participation by man, the arthropod is a mosquito and the animal is a mammal, usually a primate (other than man), but in South America there may be the minor intervention of several species of *marsupialia* and possibly some species of *rodentia.* In Africa, the forest cycle appears to be exclusively related to the monkeys although it must be conceded that the entire subject of the animal host in Africa has as yet been only superficially explored.

The mosquito vector in South America appears to be predominantly of the genus *Haemagogus,* especially *H. spegazzinii falco,* with minor contributions from *Aëdes,* notably *A. leucocelaenus.*

In Africa, the proved forest vector is *Aëdes africanus* in the area of Uganda. No virus has been isolated from forest mosquitoes in West Africa but the evidence, as far as it goes, presents nothing to contradict the thesis that *A. africanus* is the chief vector.

In all of these endemic regions, the chief mosquito vector is distinctly arboreal in habit, the greater portion of the biting population being in the foliage canopy. This would appear to relate to the more arboreal animals as the most important animal hosts.

Little is known of the population densities and life span of the important mosquitoes. For persistence of virus, the mosquitoes must be capable of living through the dry season, since none of the animal species exhibit circulating virus for more than a few days. There is presumably some level of population density below which virus propagation will not be maintained. Clearly, the insects which have had infectious blood meals must have a life span sufficient to encompass the extrinsic incubation period and give time for the delivery of a few bites after becoming infective. It is perfectly possible to have a very dense mosquito population but with a life span so short that it cannot serve to transfer virus from animal to animal.

There must be some relationship between the number of susceptible animals, the virus levels reached in the infected ones and the density of the vector mosquitoes. Small probabilities, leading to transmission failures in the laboratory, may nevertheless be adequate for continuous propagation of the virus in nature where the animals concerned may be counted by the thousands and the mosquitoes by millions. An animal with a low virus titer may have but a small chance of infecting a single mosquito; but if several thousand feed on him during the days of virus circulation even a small probability may result in there being a few capable of transmission. With a highly efficient vector, the probability of establishing another active animal infection is essentially the chance that an infectious mosquito encounter a non-immune animal in the course of feeding upon several. With an abundant animal population of modest proportion of immunity, this chance may be quite high.

There is no demonstrable threshold of infectivity so that the entire mechanism may be regarded as a probability system in which the value is never zero as long as the three components of susceptible animal host, mosquito vector and virus are present but whose value rises with the increase in density of any one of the components and becomes maximal when all three reach their highest values simultaneously or nearly so. The fact that we cannot put numerical values to these population statements indicates how much is still unknown in the epidemiology of jungle yellow fever.

The spread of virus in the forest will be compounded of the movements of host and vector. Most forest animals, especially primates, have a limited range. It is likely that wind transport of infected mosquitoes is a most important factor and there is some evidence suggesting this, but much more study is necessary.

South America

The clinical yellow fever seen in South and Central America is almost *in toto* jungle yellow fever. *Aëdes aegypti* transmission has been infrequent for many years. The opportunity to study the circumstances under which man becomes infected has been vastly better in South America than in Africa where the occasionally occurring forest infection is lost in the sea of *A. aegypti* transmitted village disease. It has long been evident that it is the people who disturb the forest during the day who fall ill of yellow fever. The woodcutters, those who cut roads and trails through the forest, the hunters, and those who clear the land for cultivation constitute the population among whom most of the cases of jungle yellow fever occur. These circumstances are made almost inevitable by the biology of the chief vector, *Haemagogus spegazzinii*. The mosquito is markedly phototropic and has its peak biting cycle in the midportion of the day. Any disturbance of the forest canopy, especially if accompanied by an increase in light, results in a vigorous attack upon any nearby warm-blooded animal. Since the usual cause of such a disturbance is likely to be man, the connection is obvious.

The mammalian host appears to be somewhat more complicated. There are great differences in the virulence of the virus for the numerous species of primates, but they are all susceptible and there are probably none that may not, under special conditions, serve as the intermediate host. It does not appear that the same species will necessarily have the same importance in different regions. In general, a primate population that has negligible mortality seems more favorable for protracted endemicity; while one that tends to exhibit high mortality and high titers of circulating virus tends to a fulminating type of outbreak which may effectively depopulate the area of the species in question.

In addition to the role of monkeys in the forest cycle, there is strong evidence that in many regions marsupials may assume the mammalian part.

Some of the species of marsupialia are quite susceptible to infection and may constitute the preponderance of the total number of infected animals. In special regions, such as the Municipio of Muzo in Boyaca, Colombia, monkeys appear to be entirely absent and in similar regions of the western slope of the Magdalena valley in Antioquia there is likewise an absence or great scarcity of any primate save man. These conditions have obtained for at least 50 years in these localities and one is forced to the conclusion that if any primate has participated in the epidemiology of yellow fever in recent times, it has been man himself. Otherwise, the zoological and immunological evidence points to marsupials such as *Metachirus* and *Caluromys* as the mammals contributing chiefly to the mammalian portion of the virus cycle. The abundance of the marsupial population together with its rapid turnover would appear to compensate for the generally higher susceptibility of the primates.

Monkey yellow fever has been demonstrated in regions devoid of human habitation; forest epidemics have occurred in regions of mixed monkey and marsupial population with some intermingling of people; endemic yellow fever has long been known in at least one area rich in marsupials with considerable human infiltration into the forest.

If one examines only single, small areas, the yellow fever virus appears rather suddenly, reaches a maximum of animal involvement in a few weeks or months and then disappears, leaving a partially immunized animal population. Several years may pass before it is again demonstrable. Such apparent discontinuity has given rise to considerable speculation that in the interval the virus must have persisted in some as yet unrecognized silent form.

When, however, careful scrutiny is given to a large region, one invariably finds that there is virus activity at some place in the area all of the time. The active front moves about, dependent upon the concordance of the necessary ecological factors such as a sufficient density of non-immune susceptible animals, an adequate population of the suitable mosquito, etc. Yellow fever, in the forest cycle of the virus, is thus endemic in the large sense but intermittent or cyclic with respect to particular regions.

The human infections, being incidental to this fundamental forest epidemiology, reflect the existing virus activity to the extent that there is human contact with the forest. A further complication is concerned with the means whereby the existence of human infections is recognized. Without a diagnostic and reporting system, there may actually be an astounding amount of severe but statistically unrecognized yellow fever. There is no one who can speak with greater feeling on this particular subject than Dr. Soper.

Africa

When one considers the problem of jungle yellow fever in Africa, a number of strikingly different conditions become evident. In the first place,

while there are great areas of South America where *Aëdes aegypti* transmission is non-existent or insignificant, there is no portion of the endemic region of Central Africa where this mosquito is not to be found in the villages. Furthermore, *A. aegypti* transmission of the virus from man to man is actually very common. There is immunological evidence that during the last war there were about 100,000 new yellow fever infections each year in Southern Nigeria alone, almost all of it unrecognized at the time. For reasons to be explained later, it appears that the probability of an individual acquiring the infection in the forest is appreciably less than in South America. Very few of the total number of recognizable cases of yellow fever are actually of jungle origin and in the presence of the vastly greater number of *A. aegypti* transmissions, there is almost no chance, especially in West Africa, of clearly associating a given case with the forest. Among many hundreds of cases of yellow fever in Nigeria and the Gold Coast, I do not know of a single one that was not obviously of the classical urban type.

The forest cycle of the virus in all of Central Africa appears to be associated with *Aëdes africanus*. Other culicines, such as *A. luteocephalus* may play an active role in some situations but in general these must be regarded as secondary. In contrast to the daytime biting habit of *Haemagogus* in South America, *A. africanus* is a crepuscular biter with its main biting peak just after sundown and a smaller phase of activity before sunrise. At dusk, the people have left the forest for their clearings and villages into which this species does not penetrate. At this time, however, the monkeys have repaired to their sleeping trees and have become quiet for the night, making excellent victims for the canopy-loving *A. africanus*. The association of the monkeys with this mosquito is thus vastly more intimate than it is with man.

The weight of evidence in East Africa is that the transfer of virus from monkey to man is mediated by *A. simpsoni* which breeds especially in banana plantings and will not only penetrate for a short distance into the neighboring forest but will enter the houses in the clearings. Certain species of monkeys are noted for their habitual raiding of the plantings and it is this situation that appears to result in the delivery of virus to man. *A. simpsoni* transmission of yellow fever in Uganda has been recognized and is probably reasonably frequent.

In contrast, *A. simpsoni* is a difficult mosquito to find in West Africa and although monkey yellow fever is widespread, the transfer to man has apparently a lower probability and true cases of jungle yellow fever are probably far less frequent than in Uganda. As banana cultivation increases in the Cameroons and Nigeria, it is possible that the yellow fever problem will become more difficult with increasing numbers of *A. simpsoni*.

The animal studies, so far as they have gone in Africa, have failed to demonstrate any participation in the forest cycles by animals other than

primates. There is a very rich fauna of this Order, varying from the tiny *Galago demidovii* to the *Gorilla*. Most of the species are diurnal but many of the lemurs are almost strictly nocturnal. There are numerous additional factors which determine whether a given species will participate in the virus cycle. The *Galago senegalensis,* for example, is fully susceptible to infection but it inhabits the savanna forest which is unsuitable for *A. africanus;* consequently, this primate plays no part in the cycle in any of the areas studied.

In other regions, such as the Sudan, epidemic yellow fever has occurred under conditions markedly different from those associated with the rain forests. Here the circumstances appear to resemble more those of rural yellow fever in Brazil and constitute a special situation by no means fully understood.

Summary

We have come to accept as well-established a fundamental forest epidemiology which, although with important differences, applies generally to both South America and Africa. Is this all? Possibly not. The history of yellow fever is one of the best examples of the dangers of being completely satisfied with an explanation that accounts for all of the known facts. It is sound science not to elaborate a theory far beyond the data; it is also important not to permit a satisfactory rationalization to stand in the way of further explorations. It is quite possible that beyond the natural cycles of the yellow fever virus which we now recognize, there are others for which at the moment we have no reliable evidence at all. Much remains to be done, especially with the dynamics of the mosquito vectors, before we have adequate understanding of the mechanisms involved in the spread of the virus through the forest and its stubborn persistence in some areas in contrast to its evanescent character in others.

YELLOW FEVER—THE SARASWATI OF VIROLOGY

DR. J. AUSTIN KERR

Director, Virus Research Center, Poona, India; Member of the Staff, International Health Division, The Rockefeller Foundation (beginning 1926). Distinguished service in many parts of the world in investigations and in applications of public health measures for the control of infectious diseases.

Saraswati is the Hindu Goddess of Wisdom and Learning and is the consort of Brahma the Creator. Saraswati is usually portrayed with four arms, which provide a convenient framework within which to discuss yellow fever virus and its relationship to the development of techniques for the study of viruses in general, and the acquisition of knowledge relative to other viruses. This subject can be discussed conveniently under four headings: virology; immunology; zoölogy; and ecology. With apologies for any liberties I may take, I am going to assign one of Saraswati's arms to each of the four disciplines I have mentioned.

Before I do that I should like to pay my personal tribute to Carlos Finlay. I would stress the fact that the acceptance of the validity of his theory that yellow fever was transmitted by *Aëdes aegypti* made it possible to eradicate yellow fever from Havana, from Cuba, from the Panama Canal Zone and from the rest of the Caribbean littoral.

The demonstration in 1901 by the U. S. Army Commission that yellow fever was due to a virus had little practical importance until the virus was captured alive and brought into the laboratory for study. This was first accomplished in 1927 and the period of eight years from then to 1935 has been described as the golden age of virology.

Virology is the first of the major disciplines to which Saraswati may be said to devote her arms. The isolation of yellow fever virus in Indian monkeys at the Rockefeller Foundation Laboratory in West Africa is one of the principal milestones of microbiology. This event, involving as it did one of the great pestilential diseases of mankind, captured the attention of investigators everywhere and greatly hastened the isolation of many new viruses in a very few years.

If one lists all the virus diseases of man, a list which is now of quite considerable length, he finds that the only human viruses which were already in captivity before the isolation of yellow fever virus were rabies, poliomyelitis and herpes simplex. Though not really a human disease, vaccinia must be added to this list because of its relationship to smallpox. Of the animal

viruses only foot-and-mouth disease had been adapted to a small laboratory animal prior to 1928.

Consider some of the viruses which have been discovered, in addition to influenza, mumps, and chicken pox, since 1927. There is a host of arthropod-borne viruses starting with those most unfortunately named "equine encephalomyelitides." These three viruses are all American; they are known as Eastern, Western and Venezuelan equine encephalomyelitis. Philadelphia is well within the region in which the Eastern virus is periodically epizoötic and epidemic.

Then there is the group of five antigenically related viruses each from a different continent, all of which appear to be transmitted by one or another species of Culex mosquito: Japanese B, St. Louis, West Nile, Ilheus, and Murray Valley. Japanese B is as common as measles in most of Japan and in many other parts of the Orient, and West Nile is equally ubiquitous in parts of Egypt, as well as being periodically epidemic elsewhere in Africa. Nor can St. Louis encephalitis virus be relied upon always to stay west of the Mississippi River.

Mention must be made of a number of viruses isolated in Africa and South America as a by-product of the studies of yellow fever. These viruses, to a total of about eleven different species, were isolated from men, mosquitoes and monkeys over a period of about ten years in the course of yellow fever studies.

The virus of Bwamba Fever was the first to be isolated by Dr. Mahaffy in Bwamba Forest. It was my very good fortune to visit Uganda for the first time last month and drive down the road at the base of Mount Ruwenzori where in 1937 Dr. Mahaffy found African road workers suffering from a febrile disease which, greatly to his disappointment, proved to be not yellow fever. He inoculated blood serum from patients into the brains of mice which he kept in a field laboratory in tents by the roadside.

Semliki Forest, Bunyamwera, Zika, Ntaya, and West Nile viruses were isolated during the next few years from either mosquitoes, monkeys or man. West Nile is perhaps the most interesting because it represents a new phenomenon: the isolation of a micro-organism before the disease it caused was recognized.

West Nile virus was isolated in 1940 in Uganda from the blood of a native woman who had a low fever and was never seen again, but it was not until 1950-51 that the disease West Nile Fever was described clinically. Two thousand miles away, in Israel, recently arrived Europeans were laid low by an epidemic of non-fatal dengue-like fever which was identified as West Nile Fever. The infection is highly endemic in the rural population of the Nile Delta in Egypt but it is so mild there that it is not identifiable clinically.

Most of these viruses are still scientific curiosities, but there is no knowing when one or another of them may become of importance as to the cause of an important new epidemic disease.

If we accept the theory that man evolved from tree shrews, lemurs, monkeys and anthropoid apes, all of which have an arboreal habitat, it seems probable that he has also inherited some virus diseases transmitted by blood-sucking arthropods. Jungle yellow fever is in this group of parasitic diseases and perhaps if we could find enough fossil mosquitoes it would be worth while looking for fossil virus particles.

Following the isolation of yellow fever virus, there was a rather intense search for animals which were highly and usefully susceptible to important viruses. This led to the discovery that the ferret—of all animals—was susceptible to influenza virus. The great usefulness of the rhesus monkey protection test in yellow fever, expensive and cumbersome though it was, stimulated the development and use of the same test in poliomyelitis, resulting in the acquisition of much information about the extent and degree of immunity to the disease which was not immediately credible.

These are two examples of the diversity of the stimulus which yellow fever gave to virology.

Both the ferret and the rhesus monkey tests are now obsolete, having been replaced almost completely by simpler and better tests, but only after they had served to unearth much basic information. The thing that made obsolete the monkey protection test for yellow fever was the discovery that yellow fever virus could be cultured in the albino mouse if one inoculated the virus directly into the brain of the mouse. The demonstration that yellow fever virus—which attacked the liver, kidney, and heart of man and the rhesus monkey—also had a neurotropic component that produced a fatal encephalitis in mice, really jarred the laboratory Brahmins of 1930.

This finding made possible the mouse protection test for yellow fever, tens of thousands of which have been done in the search for neutralizing antibody in the blood serum of man, monkeys, and other vertebrates.

Once the albino mouse was known to be susceptible to yellow fever virus, it was not very long before ways and means were found to culture other viruses, including poliomyelitis and influenza, in the mouse. Nowadays the mouse has become largely obsolete in these two diseases, but it is still the most useful of all laboratory animals in the virology laboratory.

We come next to immunology, Saraswati's second arm. Long before Carlos Finlay entered Jefferson Medical College it was generally recognized that one attack of yellow fever protected a person against the disease for the rest of his life. This belief received great support from the laboratory finding that the blood serum of a person convalescent from the disease contained large

amounts of neutralizing antibodies. Such antibodies were detected in the blood serum of persons who had suffered their attacks as many as 50 years previously, and had subsequently lived in areas in which the disease did not occur.

The original monkey protection test was used to demonstrate that the yellow fever of the Americas was immunologically as well as clinically and pathologically identical with the yellow fever in Africa — a demonstration of fundamental importance.

Mention has already been made of the fact that the development of usable protection, or neutralization, tests for yellow fever led to an intensive search for neutralizing antibodies in other virus diseases. There was a considerable degree of success in this search, and the identity of several viruses was thus established.

Early in the work with yellow fever considerable attention was given to the use of the complement-fixation test. One of the most potent yellow fever antigens is the blood serum of rhesus monkeys that are acutely ill with the disease; another excellent source is the brain tissue of mice inoculated with the virus. The complement-fixation test has proved very useful, not only in distinguishing between different viruses but also, at different levels of sensitivity, for showing relationships of viruses.

Finally, I must mention the hemagglutinating antigens of yellow fever and a number of neurotropic viruses, in which there is much interest at present. With these hemagglutinins it is possible to set up a hemagglutination-inhibition test quite similar to that of influenza, and to show that yellow fever is closely related not only to dengue virus but also to Japanese B and St. Louis viruses, among others.

I mention this matter because yellow fever is the recipient in this instance, rather than the donor. Things have come full circle, and now a phenomenon which was perfected with a very different virus is shown to be of value with yellow fever virus.

Saraswati's third arm, to continue the analogy, is the broad science of zoölogy with its two important branches: entomology and mammalogy. Studies of the reservoir of jungle yellow fever in the forests of tropical America and Africa led to a consideration of all the bloodsucking arthropods — ticks and mites as well as insects—and of all the warm-blooded vertebrates in the forests. Knowledge was scanty on many counts and the taxonomic problems were numerous both in entomology and in mammalogy. The taxonomists who performed the absolutely essential service of putting labels on insects and mammals, so that less erudite persons like doctors interested in yellow fever could be sure that they, and everybody else, knew what species they were dealing with, inherited from their predecessors much that was useful, but there were many important lacunae to be filled.

The taxonomists of today are paying off our indebtedness to Linnaeus and his contemporaries and successors by putting the taxonomy of many groups of mosquitoes and mammals into definitive order—or at least so they think. Our grandchildren will know better about this than we do.

The fourth arm of Saraswati may be said to represent the science of ecology, of which epidemiology is really only a minor subdivision. When I was a premedical student, ecology was something that girls who were majoring in botany had to take. I fear that we rather looked down on them. What the deal is today, I must confess that I do not know, but I sincerely hope that the discipline is receiving the attention which it richly deserves.

Ecology is the science which deals with the relations of organisms to their environment. The organisms may be plant, animal, or viral — giant sequoia trees, whales, or yellow fever virus. And environment means all aspects of the environment—physical and biological.

Now as far as Saraswati is concerned, all species have equal rank before her throne: yellow fever virus is just as important as *Homo sapiens.*

Ecological studies are often oriented around a single species. The epidemiologist orients his studies around man, whereas the ecologist could just as logically orient his work around a parasite that was causing trouble.

As long as there was only urban yellow fever to consider, ecological studies were rather crude. Things like the lowest temperature at which *Aëdes aegypti* could over-winter were about the upper limit of scientific elegance. But once it became evident, in South America, that jungle yellow fever was contracted in places in which there were no *Aëdes aegypti,* then ecological studies became more and more necessary, and more highly refined.

The ecological studies on jungle yellow fever revealed very conclusively that though that disease was identical with *aegypti*-transmitted urban yellow fever in all ways, except its manner of transmission, there were several different epidemiological types of the infection. Once this fact was clearly recognized in regard to yellow fever—a disease which forced itself upon everybody's attention because of its ability to kill, and to kill in horrible fashion—it served to alert the people who were working on other virus infections to the possibility that similar or equivalent factors were operative in connection with other virus diseases. Truly, yellow fever has been a model for the study of arthropod-borne virus infections.

In summary, the acceptance of the fact that yellow fever was transmitted by *Aëdes aegypti* made it possible to eradicate the disease from the Caribbean littoral. Twenty-five years later the isolation of yellow fever virus inaugurated the golden age of virology. First there was the direct stimulus to pure virology —the isolation and identification of the viruses that caused a number of important human diseases. Then the results with yellow fever led directly to

a variety of important studies in a variety of other disciplines: in immunology; in zoology; and perhaps most important of all, in ecology. These studies had to do with yellow fever, and they also had to do with other virus diseases, more or less distantly related to yellow fever. Perhaps the most important of all these contributions were those in ecology because they spurred medical investigators to get away from the classical viewpoint of man as the point of departure in their thinking. They underlined a refreshingly new point of departure: the virus, into whose orbit man was wont to wander, sometimes with very unpleasant results.

The simpler problems have been solved, in virology, in epidemiology, in ecology; the more difficult ones remain to be solved, in yellow fever as well as in general. Yellow fever virus cannot lead the pack forever. Some fine day, some other virus will provide the clue which will solve one or more of the many interesting and important questions about yellow fever which still remain to be answered. When this occurs it will be more than poetic justice; it will be scientific justice of the highest order.

ERADICATION OF THE AËDES AEGYPTI MOSQUITO FROM THE AMERICAS

DR. OCTAVIO PINTO SEVERO

Consultant to the Pan American Sanitary Bureau on *Aëdes aegypti* eradication. Formerly Chief of National Yellow Fever Service, Brazil (1932-1950). One of the world's foremost authorities on vector eradication and control.

I — TECHNICAL EVOLUTION OF THE CAMPAIGN

Initial Phase in the Control of Insect Vectors of Diseases

The confirmation in 1900 of the theory formulated by Carlos Finlay[1] nineteen years before the demonstration of the *Aëdes aegypti's* role as vector of yellow fever, substantiating the discovery of Ross[2] a few years earlier (1898) with respect to malaria transmission by the *Anopheles,* opened new paths in preventive medicine and led us to the present-day possibilities of eradicating insect-borne diseases in man.

The control, or rather the destruction, of insects which from time immemorial have caused damage, or at least annoyance, to man was undoubtedly a matter of great concern even before these events. But no thought had been given to the role the insects played, nor had any idea been gained of how to destroy them regularly and effectively. The first initiative in the Americas was taken by William C. Gorgas (1901) in Havana, Cuba,[3] immediately after the experiments made by Walter Reed and his collaborators[4] on the American Commission, under the inspiration of Finlay. Early in that same year, in South America, in a small city in the interior of Brazil (Sorocaba, São Paulo), Emilio Ribas,[5] who had long been concerned with the yellow fever problem, initiated the campaign against the *Aëdes aegypti* after learning of the first results of the Havana experiments, and following along general lines the same measures for exterminating the mosquito. Shortly thereafter (1903), in Rio de Janeiro, Oswaldo Cruz undertook an extensive campaign which, like Gorgas' work in Havana, was to pave the way for the initial technique for destroying mosquitoes.

The surprise caused by the revelation of the mosquitoes' role and the interest which it naturally aroused led at first to rather disordinate measures against the mosquitoes in their known breeding places, and in their alate stage when they took refuge in houses. Attention was turned to the *Aëdes aegypti* and the *Anopheles,* but an effective program was not evolved until the biology of the vectors became better known. Both Gorgas and Oswaldo Cruz, from

the beginning, undertook combined campaigns against the two vectors, and only later did they discover that it would be easier and more economical to combat them separately. The campaign against malaria vectors then took the direction plotted by sanitary engineering.

After the biology of the *Aëdes aegypti* became better known, the measures taken against them were aimed at attacking them in their aquatic and alate stages so as to exterminate them as rapidly as possible. For the first stage, use was made of larvicide substances with a base of mineral oils, cresols, and even potassium permanganate, as recommended by Finlay in his "plan to abolish yellow fever." Also started was the use of mechanical means to protect deposits by hermetic sealing, caulking, or screening of openings. The use of larviphagous fish was adopted when other measures could not be used. Expurgation or fumigation with sulfur fumes and volatile substances were used against the mosquito in its alate stage.

With the appearance of evidence that the *Aëdes aegypti* also was developing in abandoned deposits in yards, and even in holes in trees and crevices in plants, cleaning methods were used in such places and everything that could collect water was removed, buried or destroyed. The fundamental measure, however, was the institution of thorough inspections of houses and outbuildings. In the beginning, these inspections were not carried out systematically, following set cycles according to the biology of the mosquito, such as those later established.

In Havana and Rio de Janeiro thousands of men were recruited for campaigns that were to prove memorable, launching as they did the bases for techniques of combating the *Aëdes aegypti,* which were rapidly extended to other great cities of the Continent when the astounding results of the measures were made known.

In the United States, the success of the campaigns in Boston, New York, Philadelphia, New Orleans, and other cities which had been periodically attacked by yellow fever, is well known. In Mexico, Veracruz was freed from the disease, and in Panama it was the control of *Aëdes aegypti* and of the malaria vectors by Gorgas (1910) that permitted the construction of the Canal. In South America, yellow fever disappeared almost as if by magic from all the important sea and river ports, after the implementation of measures against the *Aëdes aegypti.*

Phase of Expectancy and Surprise in the Campaign against *Aëdes aegypti*

Impressed by the success initially achieved, Gorgas maintained that the most effective method implemented in Havana was the fumigation, but he himself was deceived as to the results of the measure in Panama. In Rio de Janeiro Oswaldo Cruz always favored the combined attack on larvae and

adults. The fact is that in 1908, when all the large cities in the Americas had already used the same measures, in the midst of great satisfaction and a certain lack of forethought, yellow fever ceased to be of concern to the public health authorities of the Americas and almost all action against the vector of the disease was abandoned.

The truce lasted twenty years, during which there were sporadic reports of the disease and a series of conjectures and theories were devised on how it should be controlled in the event it reappeared, such as those still being discussed in some countries. It was emphatically affirmed that a 5% index of infested houses provided complete safety against the invasion of the disease and that once the disease was destroyed at its key centers[6] it could never again cause concern. With this idea in mind, the Rockefeller Foundation,[7] which had devoted long study to yellow fever, took the initiative to eradicate it in the Americas by attacking it in its last strongholds, which were considered to be in Guayaquil, Ecuador, and on the east coast of Brazil, as well as the southern littoral of the Caribbean Sea. Progress was made in this period in the techniques of combating the urban vector of yellow fever, but little advance was achieved in so far as the epidemiology of the disease is concerned.

In 1928, much to everyone's great surprise and concern, an epidemic broke out in Rio de Janeiro and cases appeared also in several cities in Colombia, Venezuela, and Bolivia. The *Aëdes aegypti* infestation in the capital of Brazil had returned, perhaps, to the figure recorded prior to the work of Oswaldo Cruz, and the problem was much worse, as the city was triple its former size. It was a difficult trial for those responsible for public health in Brazil, and the losses suffered by the country were enormous. Within a few months, a veritable army of thousands of men was mobilized to attack the *Aëdes aegypti* in all its life phases and as quickly as possible.[8] All measures previously at command were put into action, some of them in an exaggerated proportion and with a certain amount of disorganization and near panic brought about by the unexpected event. The use of fumigation was abused in the attempt to prevent the appearance of new cases. But the disease persisted for almost two years, despite all efforts to extinguish it promptly. The sums of money spent would today equal tens of millions of dollars.

When the initial surprise had passed, it was seen that the former optimism had not been justified and that the calculations and conjectures regarding the extinction of the disease were not in keeping with the facts. Something was occurring that had not been taken into account, although it had been foreseen by former observers. In 1932, Soper[9] clarified the problem when he announced the existence of jungle yellow fever in Brazil (Canaan Valley).

Phase of Revelation and Optimism in the Solution of the Problem

The discovery of jungle yellow fever gave rise to the idea of eradicating the *Aëdes aegypti*. The results obtained in 1930 in the Rio de Janeiro cam-

paign and those that were being achieved since 1923 by the Rockefeller Foundation in other Atlantic port cities of Brazil, such as Niteroi Vitória, Recife, and Natal, led to the belief that the solution of the problem which arose with the discovery of the yellow fever virus in the South American forests would be possible only with the absolute eradication of the urban vector-mosquito of the disease, since the palliative control measures were no longer justified. With this end in view, the Brazilian Government, in 1932, entrusted the Rockefeller Foundation with responsibility for the campaign throughout the country, with the exception of the city of Rio de Janeiro, although later it too was included. This measure made possible the organization of a service which, as far as we know, has been the greatest ever to be undertaken against a communicable disease. In this respect, there was complete understanding on the part of the Government, which laid the financial and legal foundations for the campaign, utilizing thousands of persons trained and prepared in all parts of the country to serve with an organization devoted wholly to the problem. Working standards were instituted on the basis of (a) wise administration; (b) strict execution of the measures recommended by experience, with the compulsory use of petroleum in all deposits with foci; (c) organization of supplementary services to discover residual foci, as indicated by the capture of adults, a method that was being used against malaria and thereafter became essential to the evaluation of the anti-*aegypti* work. With the use of these three basic measures, evidence was gained that the *Aëdes aegypti* could be eradicated in Brazil with a few more years of work, if certain aspects of the problem that had been disclosed by experience were solved. The first revelation was that the success of the campaign in Brazilian port cities depended upon the application of the control measures to all other localities maintaining sea, river, or land communication with such cities, necessitating an extension of the work to the suburbs and later as far into the rural areas as *Aëdes aegypti* were found. There were regions in Brazil in which the mosquito had spread to such an extent, as was the case in the northeast, that it was necessary to cover such regions in their entirety, just as if they were a single "ever-increasing adjacent area."

Another difficulty that had to be overcome was the resistance of the *Aëdes aegypti* egg to desiccation and, in general, to temperature biologically unsuitable to other species of the mosquitoes. This resistance, which is known to reach 450 days in the laboratory, amounts to an average of more than a year under natural conditions. This is one of the factors on which the criterion of *Aëdes aegypti* eradication is based, and we shall take up this point later. The campaign that was proceeding in Brazil under the guidance of the Rockefeller Foundation was not limited to that country alone. It was extended to Bolivia, Paraguay, Peru, and Colombia, giving the same good results and showing that the eradication of the *Aëdes aegypti* was to be considered a project no longer limited to national boundaries but rather one continent-wide in scope.

The measures adopted made it possible to extend the visiting cycles from

the former intervals of 7 to 15 days, to one month, thereby affecting considerable economies and permitting, more than before, the execution of extensive eradication campaigns.

In 1940, an event occurred that convinced even the most skeptical persons of the idea of eradicating a species of mosquito. The *Anopheles (Mysomia) gambiae,* which, coming from Africa and discovered in 1930 by Shannon at Natal, in Rio Grande do Norte, Brazil, had been poorly combated and succeeded in penetrating a vast area of that State and of the State of Ceará, causing great epidemics of malaria in 1938 and 1939 and creating a problem that to many malariologists seemed insolvable. The vector was, however, conquered and eradicated in Brazil that year in a memorable campaign conducted under the guidance of the Rockefeller Foundation,[10] using the same basic principles of organization and discipline and a large group of persons who had been working actively in eradicating the *Aëdes aegypti.*

The strategy used against the *A. gambiae* was planned according to the living conditions that the mosquito had to adopt in order to survive and spread in northeast Brazil, these conditions being very similar to those of the *Aëdes aegypti* owing to the domestic habits of the adult and its preference for small collections of water. The attack was based on the systematic use of Paris green in all collections of water, and on fumigation with a compound based on pyrethrum and carbon tetrachloride in a kerosene solution (PTQ). Repeated treatments were applied to all houses so as to eliminate the greatest number of adults possible, using a De Vilbiss sprayer quite similar to those used today in DDT sprayings. Inspection was maintained of innumerable collections of water that formed and of pools that appeared in dry river beds and were used for irrigation or for watering animals. At the same time intradomicile captures were made in order to evaluate the results of the measures adopted. The eradication of the *Anopheles gambiae* in Brazil[11] demonstrated that the experience acquired and the personnel employed in the campaign against one insect vector of disease could be utilized in combating other vectors, an idea that anticipated the theory of coordinated campaigns which came about with the discovery of residual-action insecticides.

The Second World War (1939-1945), with all its horrors, provided at least one benefit in making DDT known and usable. A new stage in combating insect vectors began, and a general advance was made in anti-arthropod measures in both public health and agriculture, with the improvement of techniques and the study and utilization of other substances having residual action.

As far as we know, the first use of DDT to combat the *Aëdes aegypti* was made in 1945 in Bolivia, where it was applied in a 2% alcohol solution. Thereafter, it was used in Brazil and in other countries and became the basis of the so-called perifocal method, which has been employed ever since with absolute success. There can be no question as to the advantages derived from

the use of DDT and the opportunities it has afforded of intensifying and accelerating the eradication of the *Aëdes aegypti.*

With the advent of DDT the time arrived to give more serious thought to the eradication of *Aëdes aegypti* on a continent-wide scale. With the withdrawal of the Rockefeller Foundation from yellow fever work, the Pan American Sanitary Bureau, which had undergone a complete reorganization in 1947, inherited the responsibility for the problem. It was evident that the point demanding first attention was the eradication campaign. On the other hand, it was realized that the program that had been under way in Brazil for a number of years could not achieve complete success unless the country's frontiers and ports were fully protected against constant *Aëdes aegypti* reinfestation. It became essential to pursue on a continental scale the work that had been done within the country. In other words, an attempt had to be made to extend the campaign to neighboring countries, all countries with which communication was maintained, until the threat of reinfestation disappeared. This was what Brazil proposed to the Directing Council of the Pan American Sanitary Organization at its meeting in Buenos Aires in 1947, where the following decision was taken:

"1. To entrust to the Pan American Sanitary Bureau the solution of the continental problem of urban yellow fever, based fundamentally on the eradication of *Aëdes aegypti,* without prejudice to other measures which regional circumstances may indicate, and

"2. To develop the program under the auspices of the Pan American Sanitary Bureau, which, in agreement with the interested countries, shall take the necessary measures to solve such problems as may emerge in the campaign against yellow fever, whether they be sanitary, economic or legal."

Decisive Phase for Continent-Wide Eradication

To carry out the terms of the Directing Council's decision, the Pan American Sanitary Bureau has endeavored to use all possible means to promote and intensify the campaign in all affected countries, coordinating efforts to facilitate and hasten its success. It was principally DDT that brought that goal within reach, but a technique based on the use of that insecticide had to be evolved so as to achieve the desired results within the shortest time and at the least possible cost. From the very beginning DDT proved most effective against the *Aëdes aegypti,* but some time was lacking before the necessary norms and technical details could be established to standardize the work.

DDT, used as a larvicide merely to substitute for petroleum, would have done little to advance the campaign. It was apparent from the start that DDT could be used systematically, because of its innocuousness to man in recommended dosages, in deposits with or without water as a protection against new

foci, a protection achieved previously through complicated mechanical processes.

This method facilitated the use of the insecticide, since the worker had only to carry a container with the solution, emulsion, or suspension of DDT at 3 to 5% in order to make the application, but it has the disadvantage of attacking the mosquito only in its larval stage, thereby making little use of the residual action of the insecticide, for the organic matter usually found in home water deposits tends to reduce and even to eliminate its residual power. It was felt that the over-all application to the inside surface of dwellings, a method used in combating malaria vectors and certainly capable of eliminating all possibility of the *Aëdes aegypti's* survival, particularly when DDT is applied also to all the dwelling's containers would be too expensive and time-consuming in a campaign that, owing to its very nature, should be intensive and rapid. Therefore, preference was given to a process that was not so extensive or so expensive but could give effective results by using measures adapted to the biology of the *Aëdes aegypti.* It was thus decided that DDT should be applied in solution, emulsion, or suspension of from 3 to 5%, using a small sprayer, to both the outside and inside of all deposits, with or without water, and to a section of the nearby wall, so as to eliminate the existing foci and prevent the formation of other foci by destroying the female adults seeking to lay their eggs. This simple and economical method, which we call perifocal because it reaches the *Aëdes aegypti* in their microclimate, was adopted by the Pan American Sanitary Bureau beginning in 1948,[12] after confirmation of its effectiveness in the field.

Experience has demonstrated that with the perifocal method:

(a) one well-applied DDT treatment eliminates the *Aëdes aegypti* from small localities (less than one thousand houses) where, generally, there is no problem of hidden foci or foci difficult to reach; (b) normally, two DDT applications during a year are sufficient to solve the problem in average localities (from one to five thousand houses); (c) four carefully made applications of DDT to all infested points in a large city (over five thousand houses) at intervals of three months, are sufficient to free it from *Aëdes aegypti.*

Phase of Perfecting and Evaluating the Technique

In the succeeding phase, an effort was made to adapt the campaign to new working standards developed with the use of DDT, taking the greatest advantage possible from the experience derived from petroleum. Since the action of DDT as we have used it provides safety for at least three months, it was possible to extend the minimal visiting cycles to that period, thereby effecting considerable economies in the campaign. Moreover, as the insecticides came to be used systematically in all deposits, with or without water, providing an even greater margin of safety, it was possible also to make a considerable reduction in the complementary services concerning closed and uninhabited

dwellings, and to almost discontinue the special inspection of inaccessible deposits, control of cemeteries, and cleaning of vacant lots. Nor was it necessary to maintain the compulsory application of the law by the use of writs of infraction and fines, other than for those cases in which permission was not given to make house inspections and appropriate applications of DDT.

Other measures that have gained even greater importance with the use of DDT are the search for breeding foci difficult to reach, making captures that lead to such foci, and the compulsory use of the capture method as the final word in proving the eradication of the species in urban areas.

Another important modification that did much to simplify former ideas in this regard, was in the method of determining indices, which formerly were in every third house in all city blocks in the locality, whereas today it suffices to check every third house until the first positive one is found in each block. In small localities in rural areas it is sufficient to find one focus in order to determine what measures should be taken to eradicate the *Aëdes aegypti*. The new system adopted in this regard does not permit learning the degree of infestation, but it is sufficient to serve as a guide for using DDT.

With the reduction of the complementary services and practical discontinuance of the special services, the number of forms used to record data and to note down the measures taken was greatly decreased. From the more than one hundred forms used previously, less than ten essential ones are now being utilized.

Requirements that have not been relaxed but have been made even more rigid are those referring to the use of sketches and itineraries to direct the work in the field, to the need for demarcating work areas for each inspector, and, particularly, to the repeated and timely check work carried out not only by the chief inspectors but also by the chief or director of the campaign. The requirements also stand with respect to the use of flags to indicate the presence of an inspector or chief inspector in the house being worked and, in addition, the field personnel still must use uniforms to facilitate their work and to permit their ready identification.

After some years of experience in campaigns based on DDT, it was possible to formulate standards governing techniques and evaluation of results, these being contained in the "Guide for the Preparation of Reports on the *Aëdes aegypti* Eradication Campaign in the Americas," distributed by the Pan American Sanitary Bureau in January 1954.[13] This Guide describes the two basic reporting forms, a monthly one containing data for publication in the Bulletin of the Pan American Sanitary Bureau, and a quarterly form showing data on the initial and the present conditions in all localities found with *Aëdes aegypti* in each country. With such data it has been possible to evaluate correctly the results of the anti-*aegypti* campaign in the countries and territories where work is under way. A direct appraisal of the activities is made

by advisers and inspectors maintained by the Pan American Sanitary Bureau in the countries to instruct the local personnel and to follow up and intensify the work.

The culminating result of the use of the aforesaid standards and of the experience we have gained with the development of the anti-*aegypti* campaign in the Continent, is the criterion established for proving the eradication of the mosquito, which, along general lines, can be described as follows: Taking as relevant factors the average period that the mosquito egg resists desiccation, or about one year, and the probable duration of the residual action of DDT, estimated at three months, it has been proved that it is necessary to repeat the examination of the results in cycles, according to this residual action and within the average period that the egg is resistant. This procedure has in view to discover possible flaws in the techniques used and to permit greater reliability in the data presented, especially when the last examination is confirmed by search for capture of adults at the time the search for foci is made, in accordance with the standards adopted.

The eradication criterion for urban areas where the *Aëdes aegypti* finds all conditions favorable to survival should be as rigorous as possible, and there should not be less than two consecutive negative checks, through search for foci and for capture of adults, so as to confirm the absence of the mosquito for a period of at least one year after the last focus or the last adult was found.

In rural areas where living conditions are usually very precarious for the *Aëdes aegypti* and there are no problems concerning breeding places difficult to reach and ovular resistance can be overcome relatively easily, eradication should be confirmed after a negative check by foci search in the total number of houses at least one year after the last focus was found in the area.

Taking into account the data that are presented by the various countries and the direct appraisal of the field work, a period evaluation is made of the results obtained in the anti-*aegypti* campaign in the Americas, with a view to intensifying and improving it and to proving the eradication of the species according to the established criterion.

II — PROGRESS IN THE ERADICATION OF *AËDES AEGYPTI* IN THE AMERICAS

Determining Factors

The development of the *Aëdes aegypti* eradication campaign in the Americas dates back to the period when it was recognized that the solution of the urban yellow fever problem depended on the total elimination of the mosquito and not only on control measures to keep it within the so-called safety index of 5% of infested houses in the locality.

The initial technique of destroying mosquitoes was established early in this century by Gorgas in Havana, Cuba, and by Oswaldo Cruz in Rio de Janeiro, Brazil, after Walter Reed had confirmed Carlos Finlay's theory. The technique was based on control of the *Aëdes aegypti* in its alate stage by means of fumigation and the elimination of foci, by protecting home containers and destroying useless or abandoned containers. This method prevailed until 1915, when the Rockefeller Foundation became interested in the problem, hoping that, on the basis of the results obtained in large seaport cities considered to be key centers of the disease, eradication of yellow fever throughout the Americas could be achieved.

By 1930 great progress had already been made in the techniques of controlling the *Aëdes aegypti,* directed at their aquatic phase, with the creation of the so-called complementary services to adjust the work to certain biological peculiarities of the mosquito. Moreover, the domiciliary capture of alates had come into use as a means of directing the search for breeding foci that were hidden or difficult to reach, and of ascertaining conditions in the work area. The need was also recognized to extend the anti-*aegypti* work to all localities linked by land, sea, or river communications, as well as to intermediate localities into which the mosquito could penetrate by being transported in vehicles, carried in larval form in containers, or by its own flight.

With the discovery by Soper in Brazil (1932) of jungle yellow fever, it seemed evident that, if complete protection was to be afforded to urban populations, the solution of the problem depended on absolute eradication of the *Aëdes aegypti.* It was then that the Rockefeller Foundation established with the cooperation of the Government of Brazil an organization that permitted the development of a systematic and intensive campaign against the *Aëdes aegypti,* based on the compulsory use of petroleum in all containers with foci, and on technical and administrative principles which served as an example for other campaigns against this and other insects organized in Brazil and in other South American countries, and which still serve us as a guide in the continental *Aëdes aegypti* eradication campaign.[14] As the work was carried on by the Rockefeller Foundation until 1940 and thereafter under the exclusive direction of the Government in Brazil, the mosquito was eliminated in vast areas covering some three million square kilometers, thereby reducing to a third the problem of *Stegomyia* infestation in that country.

Good results were obtained also in Bolivia, Colombia, Ecuador, Paraguay, and Peru in campaigns conducted under the auspices of the Rockefeller Foundations[15] until 1940, when that institution withdrew from its participation in the problem.

With the advent of DDT, the idea of eradication grew in scope, commanding attention no longer on a nation-wide but on a continent-wide scale. In September 1947, the Directing Council of the Pan American Sanitary Or-

ganization, meeting in Buenos Aires, on the proposal of Brazil, approved a resolution entrusting the Pan American Sanitary Bureau with "the solution of the continental problem of urban yellow fever, based fundamentally on the eradication of *Aëdes aegypti.*"

Since 1947, the Pan American Sanitary Bureau has expended all possible efforts to promote and intensify the campaign in all affected countries, establishing cooperative agreements to assist them by providing personnel and material, for which purpose it has had the cooperation of TA/WHO, UNICEF, and the Institute of Inter-American Affairs.

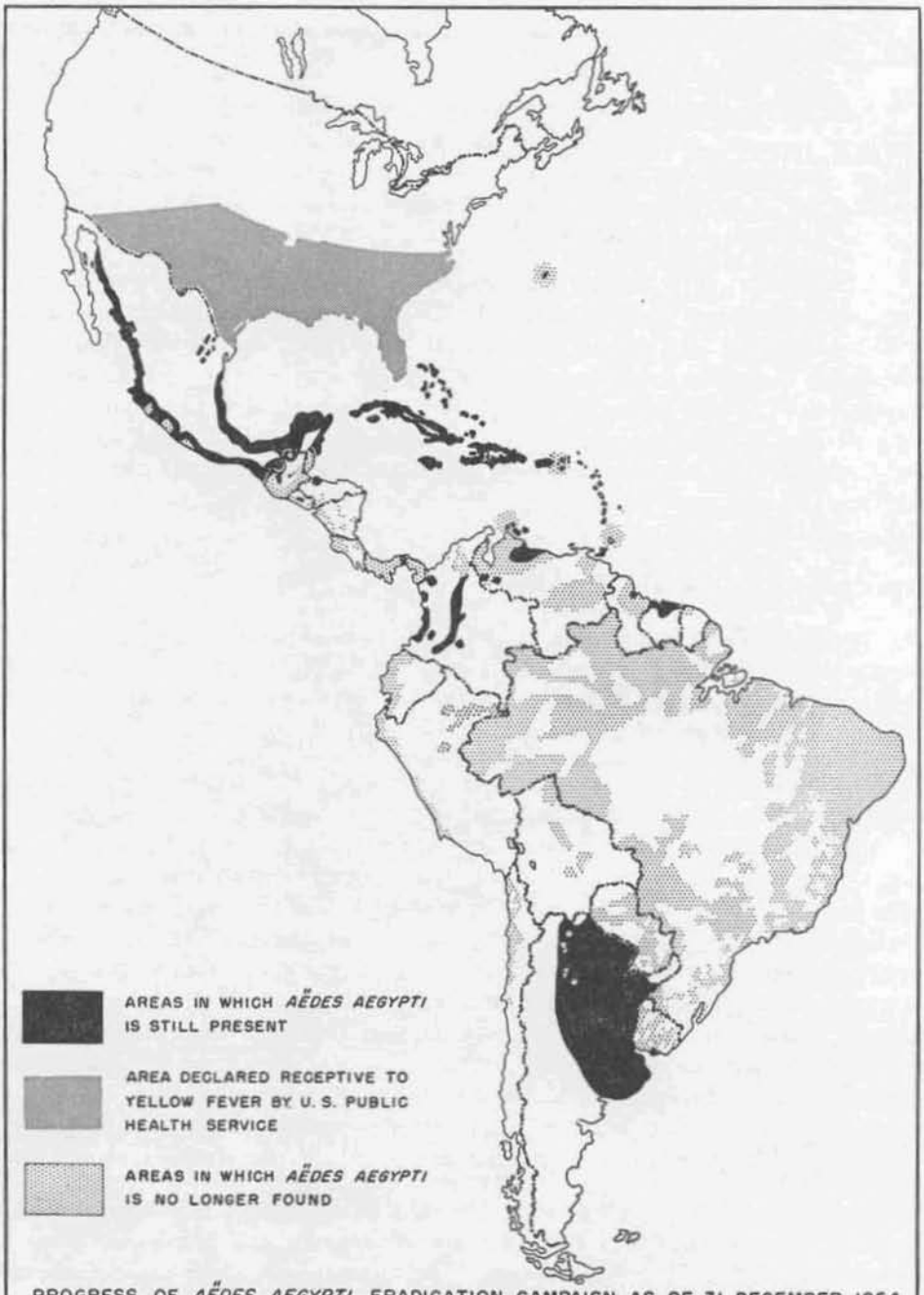
The strategy adopted for the continent-wide campaign, planned according to circumstances and to meet the more urgent needs in countries that had done little or nothing against the *Aëdes aegypti,* was aimed initially at protecting the areas most threatened by an invasion of the jungle virus in South America, and later in Central America and Mexico. The attack was then directed to the sources of spread of the mosquito in almost all islands of the Caribbean, there remaining now to be undertaken the final phase of expansion and extension of the campaign to all areas of the Americas where the *aegypti* finds conditions favorable to survival.

Panoramic View of the Problem

The progress made in the *Aëdes aegypti* eradication campaign in the Continent is reflected in the attached map, based on reports until December 1954 and on first-hand observation of the problem in each country. The results can be summarized as follows:

South America: The vast area in the eastern and northeastern part of Brazil treated for many years with petroleum, was shown in 1952, after four years of systematic DDT work, to be almost completely clean, and only the final checks are lacking to prove eradication of the *Aëdes aegypti* throughout the country. The problem in Brazil, because of the country's area and existence of conditions favorable to the mosquito, undoubtedly represented one half of the problem in the Continent. Bolivia, in 1948, was the first country to be freed of the mosquito, French Guiana followed in 1952. Chile, Ecuador, British Guiana, Paraguay, Peru, and Uruguay, in that region of the Continent, are in the final stages of eradication. Argentina is now organizing a nation-wide campaign. In Colombia and Venezuela the work continues and is being intensified in Venezuela after the recent jungle virus threat. Surinam is the only part of South America where the campaign has not yet been started.

Central America: Subject to the results of the last checks now being made, Panama, Nicaragua, Costa Rica, Honduras, and British Honduras can be considered to be in the final stages of their campaigns. The campaign was intensified recently in El Salvador and Guatemala and the final stage should be reached next year. The *Aëdes aegypti* is considered to be eradicated in



PROGRESS OF *AËDES AEGYPTI* ERADICATION CAMPAIGN AS OF 31 DECEMBER 1954

the Panama Canal Zone (U.S.A.), although no statistical data are available to corroborate this fact.

Greater Antilles: Generally speaking, the situation in these islands is still not satisfactory. Cuba, where the idea of combating the *Aëdes aegypti* originated, is quite infested as was revealed by the first results of the campaign initiated in March 1954. In the Dominican Republic the situation is better in the interior than in the capital, where it has not yet been possible to apply all the necessary measures. Nor has Haiti succeeded in developing a rapid plan of work. Jamaica is still infested, but measures are being taken to improve the campaign. Good results are being obtained in Puerto Rico with the measures adopted to accelerate the eradication of *aegypti.*

Lesser Antilles: In most of these small islands the campaign was initiated recently and there is a trend to extend it to the others. They include thirteen archipelagos, in ten of which *Aëdes aegypti* work is already being conducted, although not always in satisfactory fashion. With respect to the spread of the mosquito, Trinidad, Tobago, and the Netherlands West Indies (Curaçao, Aruba and Bonaire) are the most important points and they are now adopting measures that should result in the speedy elimination of the *Aëdes aegypti.* In Trinidad an outbreak of yellow fever occurred last year, when the virus invaded Port-of-Spain, producing *Aëdes aegypti*-transmitted cases, a fact that had not occurred in the Americas for over twelve years.

North America: In Mexico, the campaign that had been interrupted in 1953 was resumed in 1954. There are large infested areas in that country, particularly in the Yucatan Peninsula and along the Atlantic and Pacific coasts. It is expected that the recently initiated malaria-eradication campaign, with the application of DDT to large areas where the two problems coexist, will contribute much toward eliminating the *Aëdes aegypti.*

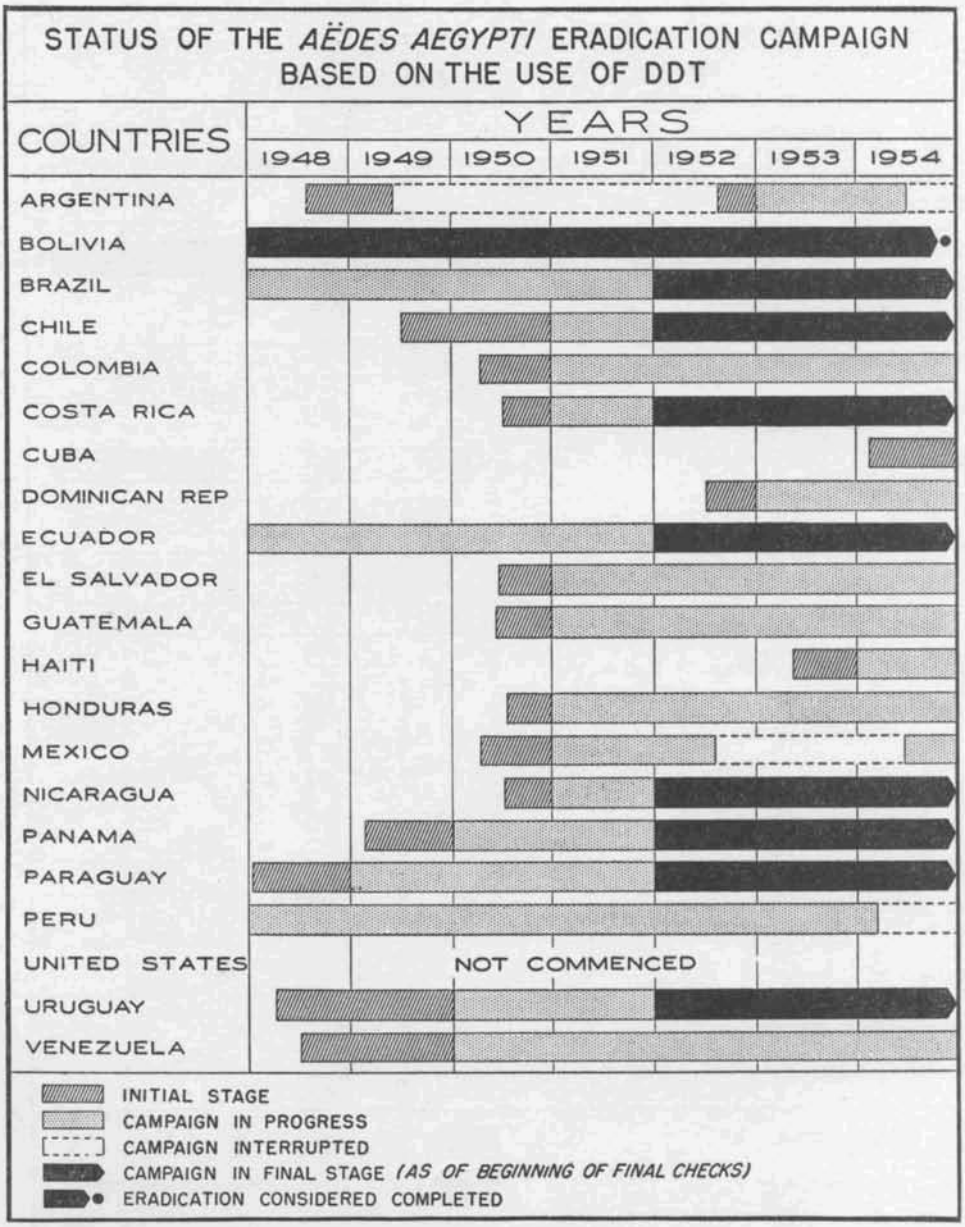
Special reference should be made to the United States, the only country that has not initiated an *Aëdes aegypti* eradication campaign. Ponderable reasons, some acceptable, others unjustifiable, have been postponing the start of the campaign in this country, which is in a position to carry it out quickly and brilliantly. The problem has more of a psychological basis and is difficult to solve from a political viewpoint. In view of the vast area considered as yellow-fever receptive by the Public Health Service,[16] an area that includes part or the total territory of eighteen states in the south of the country, the task would be a difficult one to undertake, particularly in its initial stage, but there are many factors that tend to facilitate the campaign. Among them we can point out the interest being shown by the Communicable Disease Center and the willingness of the Government to make a study of the problem next year, beginning at the important seaports.

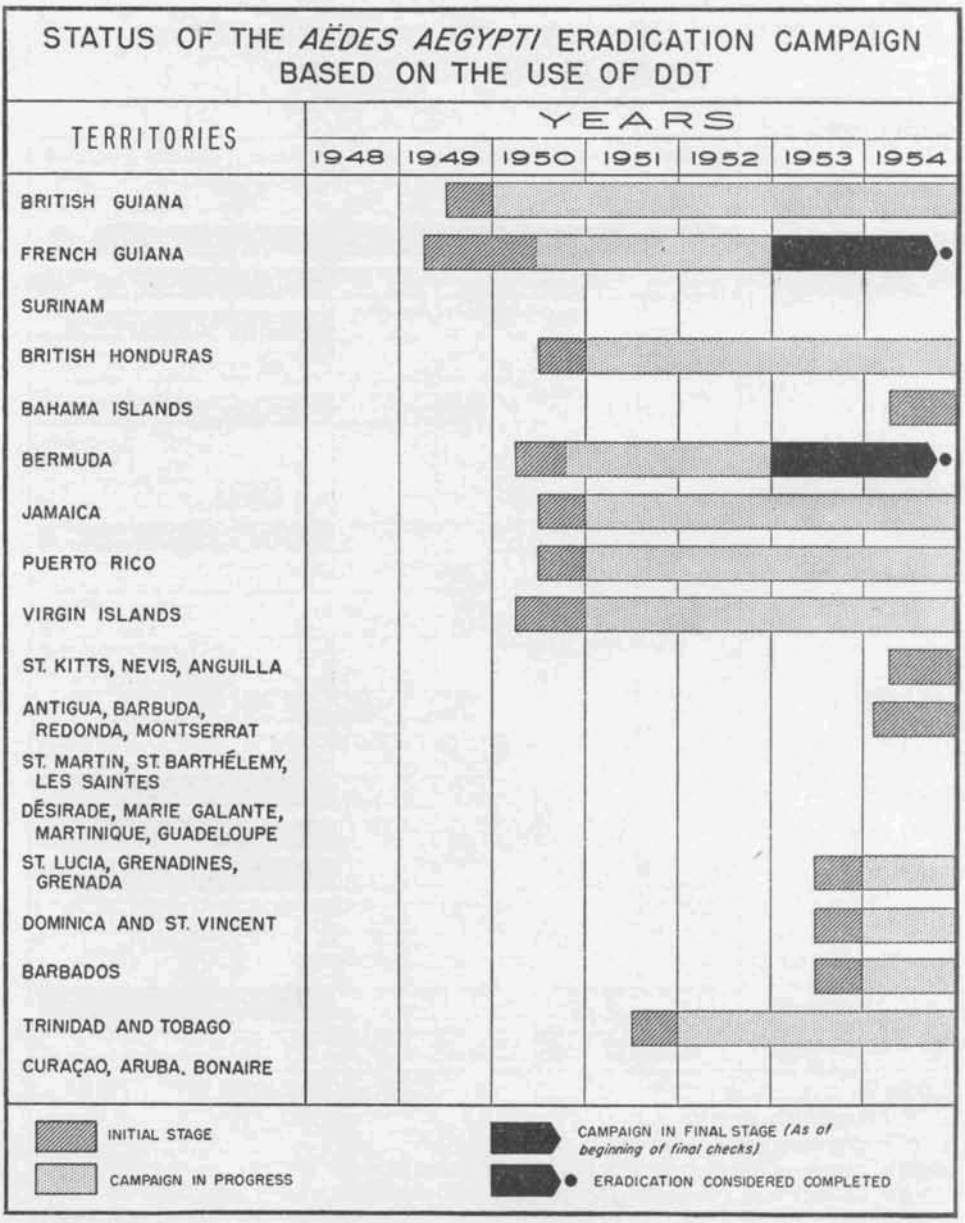
EXTENT OF THE PROBLEM AND CUMULATIVE RESULTS OF THE ANTI-AEGYPTI CAMPAIGN IN THE COUNTRIES AND TERRITORIES OF THE AMERICAS THROUGH JUNE 1955 OR LATEST REPORTED MONTH *

Country or Territory	Reported month	Extent of the problem in square kilometers			Number of localities covered						To be reinspected
		Total area of the country	Initial area presumably infested	Area inspected to date	Preliminary survey		Total infested treated	Post-treatment inspection			
					Total	With *A. aegypti*		Total	No *A. aegypti*	With *A. aegypti*	
NORTH AMERICA											
Mexico	VI.55	1.969.367	1.000.000	100.000	897	471	471	412	253	159	59
CENTRAL AMERICA											
Costa Rica	VI.55	51.011	20.000	20.000	1.220	104	104	104	104	0	
El Salvador	VI.55	34.126	18.675	12.431	889	187	187	185	173	12	2
Guatemala	V.55	108.889	36.881	6.713	1.471	138	138	121	116	5	17
Honduras	XII.54	112.088	40.000	12.000	593	53	53	53	53	0	
Nicaragua	VI.55	148.000	65.263	63.762	2.939	18	18	18	18	0	
Panama	VI.55	75.475	40.000	23.929	1.050	41	41	40	4	0	1
British Honduras	V.55	22.965	10.360	7.770	36	2	2	2	2	0	
CARIBBEAN ISLANDS											
Cuba	VI.55	114.254	80.000	255	12	11	11	7	6	1	4
Haiti	VI.55	27.750	25.000	4.000	1.542	464	464	294	262	32	170
Dominican Rep.	VI.55	48.734	42.020	33.780	1.069	219	219	115	103	12	104
Antigua	VI.55	280	280	280	43	37	37				37
Aruba	I.55	181	114	114	128	128	128	5		5	123
Bahama Islands	VI.55	11.404	11.404	28	2	2	2				2
Barbados	V.55	431	431	404	93	93	14	12	3	9	81
Barbuda	VI.55	161	14	14	1	1					1
Curacao	VIII.54	450	70	37	59	59	30	30	4	26	29
Grenada	VI.55	344	344	344	10	10	10	10	9	1	
Jamaica	V.55	11.424	11.424	8.835	14	14	14	14	1	13	
Martinique	VI.55	1.100	900	900	33	33	17	17	15	2	16
Puerto Rico	VI.55	8.896	8.896	5.496	478	213	213	213	100	113	
St. Kitts-Nevis-Anguilla	IV.55	396	396	396	24	24	24	24	16	8	
St. Lucia	VI.55	603	259	259	24	24	24	24	22	2	
St. Vincent	VI.55	389	363	**	7	7	7	3	1	2	4
Trinidad & Tobago	VI.55	5.218	3.108	3.108	129	114	114	66	8	58	48
SOUTH AMERICA											
Argentina	V.55	2.808.492	1.500.000	93.000	199	21	21	11	10	1	10
Bolivia	IX.54	1.098.581	100.000	100.000	282	65	65	65	65	0	
Brazil	IV.55	8.516.037	5.358.822	8.240.026	259.363	36.202	36.202	36.202	36.200	2	
Colombia	VI.55	1.138.355	280.000	171.000	2.105	305	305	303	301	2	2
Chile	III.55	741.767	50.000	50.000	81	44	44	44	44	0	
Ecuador	VI.55	275.000	69.454	100.000	2.811	337	337	337	337	0	
Paraguay	VI.55	406.752	200.000	1.561	98	98	98	98	98	0	
Peru	III.55	1.311.030	714.000	638.000	4,320	191	191	191	191	0	
Uruguay	VI.55	186.926	186.926	186.000	1.007	133	133	133	133	0	
Venezuela	V.55	912.050	600.000	485.000	2.092	197	197	141	123	18	56
British Guiana	V.55	214.962	4.662	4.662	93	93	93	93	92	1	
French Guiana	VI.55	91.000	91.000	91.000	222	55	55	55	55	0	

*Bermudas, St. Croix (U. S. Virgin Islands) and Panama Canal Zone state that *A. aegypti* has been eradicated from their territories. Montserrat, Redonda and Sombrero in the Leeward Islands, St. John and St. Thomas in the U. S. Virgin Islands, and Dominica in the Windward Islands are carrying out campaigns but no reports are available. *A. aegypti* is present but no campaign has yet begun in the United States, Bonaire, Saba, St. Eustatius and Southern St. Martin in the Netherlands Antilles; Guadeloupe, Desirad, Les Saintes, Maria Galante, St. Bartholomew and Northern St. Martin in the French Antilles; and Anegad, Jost Van Dykes, Tortola and Virgen Gorda in the British Virgin Islands.

**Information not available.


STATUS OF THE AËDES AEGYPTI ERADICATION CAMPAIGN
BASED ON THE USE OF DDT
COUNTRIES
YEARS
1948
1949
1950
1951
1952
1953
1954
ARGENTINA
BOLIVIA
BRAZIL
CHILE
COLOMBIA
COSTA RICA
CUBA
DOMINICAN REP
ECUADOR
EL SALVADOR
GUATEMALA
HAITI
HONDURAS
MEXICO
NICARAGUA
PANAMA
PARAGUAY
PERU
UNITED STATES
NOT COMMENCED
URUGUAY
VENEZUELA
INITIAL STAGE
CAMPAIGN IN PROGRESS
CAMPAIGN INTERRUPTED
CAMPAIGN IN FINAL STAGE (AS OF BEGINNING OF FINAL CHECKS)
ERADICATION CONSIDERED COMPLETED


STATUS OF THE AËDES AEGYPTI ERADICATION CAMPAIGN BASED ON THE USE OF DDT
TERRITORIES
YEARS
1948
1949
1950
1951
1952
1953
1954
BRITISH GUIANA
FRENCH GUIANA
SURINAM
BRITISH HONDURAS
BAHAMA ISLANDS
BERMUDA
JAMAICA
PUERTO RICO
VIRGIN ISLANDS
ST. KITTS, NEVIS, ANGUILLA
ANTIGUA, BARBUDA, REDONDA, MONTSERRAT
ST. MARTIN, ST. BARTHÉLEMY, LES SAINTES
DÉSIRADE, MARIE GALANTE, MARTINIQUE, GUADELOUPE
ST. LUCIA, GRENADINES, GRENADA
DOMINICA AND ST. VINCENT
BARBADOS
TRINIDAD AND TOBAGO
CURAÇAO, ARUBA, BONAIRE
INITIAL STAGE
CAMPAIGN IN PROGRESS
CAMPAIGN IN FINAL STAGE (As of beginning of final checks)
ERADICATION CONSIDERED COMPLETED

Evaluation of the Campaign

In the first three columns of the attached table an attempt is made to evaluate the extent of the problem in each country, on the basis of knowledge of the areas presumed to be infested since they present conditions favorable to the *Aëdes aegypti,* as compared with the total area of the country and the already inspected area in which the activities were carried out, figures for the latter being given in the other columns of the table.

To show the evolution of the *Aëdes aegypti* eradication campaign in the Americas, we have presented one chart including all the countries and another for the non-self-governing territories. As regards the number of countries and territories undertaking this work, it can be seen that, from 1948 to 1954, the number of countries rose from 4 to 20 and that of territories from 0 to 14 in 1954 out of a total of 18 territories. Thus, only one country and four territories are still lacking to complete the effort that sooner or later will bring about the continental eradication of the urban vector of yellow fever in the Americas.

Indeed, the campaign is showing constant improvement, being pursued according to the standards derived from former experience with the use of petroleum, now much more simplified through the profitable use of DDT, with the result that all the work is done with greater speed and economy.

The strict application of the standards set forth in the "Guide for the Preparation of Reports on the *Aëdes aegypti* Eradication Campaign in the Americas," published by the Pan American Sanitary Bureau in January 1954, and the adoption of the criterion for proving eradication, provide a good basis for confidence in the results that are being recorded. Eradication cannot be regarded as proved before a period of at least one year of absence of *Aëdes aegypti,* during which three negative checks have been made, the last of these accompanied by the search for capture of alates. In rural areas where there is little possibility for the mosquito to resist the action of DDT, a single check made after one year can be accepted, so long as the check includes all the buildings in the area.

The final word in declaring the *Aëdes aegypti* to be eradicated in a country or territory would certainly have to be given by the Pan American Sanitary Bureau, which reserves the right to have supplementary checks made directly under its supervision. This is what has just occurred in Paraguay, where, in the presence of the campaign adviser, the final check was made in spots where there was still some possibility of finding *Aëdes aegypti* in Asunción, once one of the most highly infested cities in the Continent and today completely free, as is the rest of Paraguay. The countries in which the final check is next to be made are: Chile, Ecuador, Peru, Uruguay, in South America; and Panama, Nicaragua, Costa Rica, Honduras, and British Honduras, in

Central America. In the near future Brazil also will require this final check to be declared free from the *Aëdes aegypti*. There is a thorough understanding on the part of the public health authorities in this respect, because the Pan American Sanitary Bureau, as an organization belonging to all countries of the Americas, utilizes for its activities technical personnel of various nationalities, in a practical demonstration of Pan-Americanism.

REMARKS

As was the case in the past with yellow fever and even more so after the revelation of the *Aëdes aegypti's* role in transmitting the disease, only the presence of the virus or the immediate threat of it has been able to arouse those responsible for the protection of exposed populations, causing real panic and the adoption of emergency measures that no longer are compatible with the attitude that should prevail with respect to prevention of communicable diseases. For, unfortunately, even today not every one is convinced that eradication of the *Aëdes aegypti* affords the only effective protection to all the Americas against the menace of jungle virus. Vaccination, which since 1937 has proved to be an excellent measure for protecting populations threatened by the jungle virus, does not provide complete safety, since it does not reach everyone and it is not economical because it requires periodic repetition.

The great advance made in the campaign in South America and now also in Central America was to a large extent brought about as the result of jungle yellow fever epidemics that occur frequently in the first region and that, in 1948, became a source of concern in the latter, for since that date the jungle virus has been appearing in sporadic outbreaks and its northward advance arrived at the Honduras-Guatemala border last year.

The fact that not a single case of yellow fever caused by the *Aëdes aegypti* has occurred in the countries that are regularly carrying out campaigns against the mosquito, can be taken as evidence of the effectiveness of the measures adopted.

A real impact was produced late last year by the outbreak of yellow fever on the island of Trinidad, from where the disease had been absent for more than forty years and where the measures against the *Aëdes aegypti* had been inadequate, with the result that cases transmitted by that mosquito occurred in Port-of-Spain. Another occurrence that merits serious thought was the case of yellow fever that was transported by plane in October of last year from the interior of Venezuela to Caracas, capital of the country, causing a real panic and giving rise to extreme measures by the authorities, who went so far as to spray DDT from airplanes and to use fumigation and other spectacular measures, in an attempt to pacify the population, whose state of mind was close to that reached by the inhabitants of Philadelphia in 1793, as was so well described by J. H. Powell[17] (Bring Out Your Dead).

Such occurrences should no longer take place in our times, considering the weapons we now have to combat and eradicate *Aëdes aegypti* throughout the Continent. This objective is justified not only because the mosquito is the urban vector of yellow fever and of dengue, but also because the work represents an important contribution to cooperation and security in the field of continental public health.

With the constant increase in air traffic, no country can really be considered to be protected so long as the possibility of reinfestation by the *Aëdes aegypti* exists, and, if for no other reason, the mosquito should be eliminated as a dangerous "export product."

In considering the progress made in the *Aëdes aegypti* eradication campaign, we should take into account also the collateral benefits it has brought to many countries of the Americas. Suffice it to point to what happened in Brazil some years ago when, in the *Anopheles gambiae* eradication campaign, so much was done toward organizing the services against malaria and plague by using the personnel and technical and administrative standards of the former yellow fever service created by the Rockefeller Foundation.

In organizing the present campaign based on DDT, thought is given constantly to the possibility that, after the *Aëdes aegypti* is eradicated, the structure can be used in establishing other campaigns against insect vectors, as is being done in Uruguay, where the anti-*aegypti* personnel will be utilized to combat triatomes, vector of Chagas' disease.

On the other hand, the use of DDT against malaria vectors, especially in Central America, has contributed much toward the eradication of *Aëdes aegypti* wherever the two problems coexist. There is thus a double reward to be gained from the resolution adopted by the Pan American Sanitary Conference at its meeting in Santiago, Chile, in October 1954, which recommended the intensified use of that insecticide to eradicate malaria before the resistance to its lethal action becomes manifest. In the final analysis, the eradication of the *Aëdes aegypti,* just as the elimination of malaria in the Americas, is a goal from which we should never again be swayed, after having reached the vantage point we now hold.

The campaign to eradicate the *Aëdes aegypti,* with its extension to practically the entire Continent and the noteworthy results that have been achieved, can perhaps be considered as one of the greatest undertakings yet to be pursued in the field of public health, for the solution of a problem of continent-wide concern. To contribute toward this undertaking and toward the extension of its benefits in the future, with the perseverance and foresight inspired by the example of Carlos Finlay, is a source of justifiable pride for all of us who, for so many years, have devoted ourselves to this campaign.

For more than half a century the fight against the *Aëdes aegypti* has been waged in the Americas, and although there have been disappointments and mistakes, there also have been the rewards of great success. For more than twenty years we have felt certain that the eradication of the mosquito is possible and for some eight years we have been engaged in this continent-wide campaign that has already solved at least two-thirds of the problem. The final success now depends, more than ever before, on what is decided in this great country.

SUMMARY

The first part of this paper presents a brief review of the evolution of measures to control the insect vectors of yellow fever and malaria, starting at the turn of the century with the confirmation of Finlay's theory on the role of the *Aëdes aegypti* in yellow fever transmission and the definition by Ross and Grasi of the *Anopheles'* role as malaria vectors. Reference is made to the early campaigns of Gorgas in Havana and Oswaldo Cruz in Rio de Janeiro to combat these two mosquitoes, using the fumigation method for the alate stage and mineral oils for the larval stage, together with the protection or destruction of deposits. An account is given of how the control measures used also in other large port cities brought about the apparent disappearance of the disease in almost the entire Continent by the year 1908. Mention is made of what was done in the interval until yellow fever reappeared in Rio de Janeiro in 1928, when attention was attracted to certain epidemiological aspects of the disease, leading Soper, in 1932, to the discovery of the sylvatic aspect of yellow fever, and showing that the solution of the problem lay in the eradication of the *Aëdes aegypti*. It was demonstrated, in campaigns conducted in several South American countries under the auspices of the Rockefeller Foundation, that eradication was possible with the use of technical and administrative measures based on systematic inspection of dwellings and compulsory application of petroleum to deposits containing foci.

Reference is then made to the decisive phase for *Aëdes aegypti* eradication in the Americas, which began with the advent of DDT and the turning over of responsibility for the problem to the Pan American Sanitary Bureau in 1947.

It is shown how the campaign was extended to almost all the countries and territories, with the aid and collaboration of the Bureau and contributions from TA/WHO, UNICEF, and IIAA. Stress is laid on the value of the technical standards adopted, which are based on the application of DDT by the perifocal method. It is shown how these standards permitted the establishment of a criterion for proving eradication, based on the residual action of DDT and on the biology of the *Aëdes aegypti,* together with a periodic evaluation made of the results, the latter being considered generally very satisfactory.

The second part of the paper presents a summary of the progress of the campaign, describing the results obtained in the various countries and territories, as depicted in the map showing the areas considered to be free as well as those still infested. Also included is a table presenting the statistical data that serve as the basis for the evaluation, together with two bar charts showing the evolution of the eradication campaign from 1948 to 1954 in the various countries and territories.

Finally, there is a commentary on certain aspects of the problem that are not yet fully understood, and the reasons are pointed out why the *Aëdes aegypti* eradication campaign in the Americas has not yet achieved the success that was to be expected.

Bibliography

1. Finlay, Carlos: "El mosquito hipotéticamente considerado como agente de transmisión de la fiebre amarilla," *An. Acad. Cien. Med.* (Havana), *18:*147-169, 1881.
2. Ross, Ronald: "Preliminary Report on the Infection of Birds with Proteosoma by Bites of Mosquitoes," Gov't. Press, Calcutta, Oct. 11, 1898.
3. Gorgas, William C.: "Sanitary Conditions as Encountered in Cuba and Panama and What is Being Done to Render Canal Zone Healthy," *Med. Rec.*, p. 10, 1905.
4. Reed, W., Carroll, J., Agramonte, A., and Lazear, J. W.: "The Etiology of Yellow Fever—Preliminary Note," Phila. M. J., *6:*790-796, 1900.
5. Ribas, Emilio: "Profilaxia da Febre Amarella," 5º Con. Bras. Med. e Cirurgia, June 27, 1903.
6. Carter, H. R.: "Mechanism of Spontaneous Elimination of Yellow Fever from Endemic Centers," *Ann. Trop. Med., 13:*299-311, 1920.
7. Connor, M. E.: "Suggestions for Developing Campaign to Control Yellow Fever," *Am. J. Trop. Med., 4:*277-307, 1924.
8. Fraga, C.: "A Febre Amarela no Brasil, 1930," Of. Gr. Insp. Dem. Sanitaria, Rio de Janeiro.
9. Soper, F. L.: "Jungle Yellow Fever; New Epidemiological Entity in South America," 1936.
10. Soper, F. L., and Wilson, D. B.: *"Anopheles gambiae in Brazil,"* the Rockefeller Foundation, N. Y., 1943.
11. Soper, F. L., and Wilson, D. B.: "Species eradication," *Jour. Nat. Mal. Society,* 1942.
12. Severo, O. P.: "Contribución al Control del *Aëdes aegypti* con Mira a su Erradicación Continental," *Bol. Of. San. Pan., 27:*1045-1056, 1948.
13. Severo, O. P., and Gutierréz, R. I.: "Bases tecnicas y normas de evaluación de la campaña contra el *Aëdes aegypti," Bol. Of. San. Pan.,* 36:537-557, 1954.
14. Soper, F. L., Wilson, D. B., Lima, S., and Antunes, W. S.: "The Organization of Permanent Nation-wide Anti-*Aëdes aegypti* Measures in Brazil, 1943," The Rockefeller Foundation, N. Y.
15. Strode, George K., and cols.: "Yellow Fever," McGraw-Hill Book Company, Inc., N. Y., 1951.
16. Bradley, G. H., and Hatchley, F. O.: "The *Aëdes aegypti* situation in the United States," New Jersey Mosquito Extermination Association, 1953.
17. Powell, J. H.: "Bring Out Your Dead—The Great Plague of Yellow Fever in Philadelphia in 1793," University of Pennsylvania Press, 1949.

YELLOW FEVER IN CENTRAL AMERICA

The Post-War Spread as a Threat

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Among the triumphs which man occasionally shows in his relentless fight against the powers of a hostile environment, few have had more decisive historical repercussions over a wider geographical area than that which followed Carlos Finlay's trail-blazing discovery. Perhaps with the exception of plague, no scientific finding has ever resulted in such efficient, definitive methods of prevention.

The success of the campaigns which were undertaken, once the new notion of the insect vector was established, changed the destiny of the tropics: it allowed its inhabitants to plan their lives without the reservations which in the past the ever-existing possibility of the yellow fever epidemic imposed upon them. An era of optimism began, substantiated by the fact that the great tragedies of previous centuries became more and more rare. A few mysterious outbursts (happening away from the coastal areas or in the absence of any known source of contagion) failed to shake the belief that, by keeping the *Aëdes aegypti* population below certain defined limits, the probability factor of urban epidemics was reduced to negligible proportions.

It was not until the discovery of a new epidemiological and epizoötical mode of the disease that some dogmatic assertions had to be re-examined. On the one hand, the suddenly revealed evidence of permanent sources of infection in the forests of Africa and South America, and on the other hand the increase (both in speed and in intensity) of human traffic brought by air transportation, suggest that this is an opportune moment to reconsider some notions about preventive measures.

In the face of a permanent local and international menace, incomplete measures of partial control are perhaps no longer adequate. The probability factor is entirely different from that which might depend on intermittent infectious foci. And it has become dangerous, up to a certain point, to rely for one's safety on control measures taken by neighboring nations.

The past few years have emphasized the validity of this point of view. An unexpected epidemiological episode has shown to what extent conditions (believed until then to be limited to a specified geographical region) may suddenly break out and endanger other regions until then happily dozing in a state of false security. I am referring to the Middle American wave of yellow fever, which it is my purpose to relate briefly here. I shall endeavor to integrate it into the long story of which it is nothing but a chapter, and to underline the lessons which can be drawn from the observation of its course.

The theater of this event: the tropical rain forests and the deciduous forests of Panama, Costa Rica, Nicaragua and Honduras. The time: late 1948 to mid 1954.

Prior to 1948, there was evidence from immunological surveys of sylvan yellow fever in humans in the area east of the Panama Canal. On the other hand, the results of the surveys conducted west of the canal were interpreted as indicating the absence of the sylvan form of the disease in Middle America.

The first confirmed case of yellow fever west of the Canal occurred in January 1950. In April 1951 further cases were reported from Almirante, close to the Costa Rican border, and throughout that year the disease spread out in that country. In July 1952 confirmed cases occurred at the headwaters of the Rama river in Eastern Nicaragua.

From the beginning of the occurrence of human cases, a heavy mortality had been observed among the simian population of the countries involved. Livers of specimens pertaining to the genuses *Alouatta* (howler monkey) and *Ateles* (spider monkey) found dead in the forest showed specific lesions of yellow fever. The primate fauna was virtually exterminated, with the exception of monkey species of the *Cebus* genus, which is susceptible to yellow fever, but survives the disease. The observation of manifestations among the monkey fauna became therefore the most efficient way of following the trajectory of the phenomenon, especially when it traversed large sectors of uninhabited forest.

Surveys of monkey immunity afforded good indications as to the immediate history of the region and permitted in certain cases to predict the future. The usefulness of this observation was enhanced by the fact that intense campaigns of vaccination were undertaken by the countries involved, with the result that human cases became more and more rare as the wave progressed towards the north.

As it reached Nicaragua the wave split in two fronts; one of them progressed through the deciduous tropical forests situated west of Lake Nicaragua, the other invaded the tropical rain forests of the East. The progression of these two waves was not comparable, since the seasonal and climatic conditions are different in the two geographical areas. Whereas the Pacific slopes

of the West are in the theater of prolonged dry seasons lasting from October to May, the forests of the East show only a short interruption in the yearly curves of rainfall. Whereas the mosquito fauna of the West disappears for several months, in the East specimens of known vectors are to be found throughout the year. As was to be expected, the progression of the wave in the latter region was a continuous and uninterrupted phenomenon; on the Pacific side, on the contrary, there was at least one interruption in the course of the wave; it coincided with the disappearance of mosquitoes in the first months of 1953; the infection remained latent under conditions not yet quite clear and to be discussed later. Following the onset of rains, monkey mortality started anew at the very place where it had stopped several months earlier, and the local wave progressed northward for a while and died in the vicinity of Managua at the end of the same year. To the East the virus invasion raged along the foothills and headwaters, reached the Patuca valley and, by December 1953, emerged into Honduras, at the headwater of the Guampu, a northern affluent of the Patuca. From there on, it progressed during the first half of 1954 in a northerly and westerly direction, the wave reaching the Ceiba zone through Piedras Amarillas and Yaruca. In May, June, July and August, monkeys were dying on the flats of La Masica, Benque, and San Francisco, on the northern side of the coastal mountain range. The last positive monkey liver was obtained from that region in mid-August. No further evidence has been obtained north or west of that region, and it would seem now that the wave is stalled for the time being. Nevertheless, the experience gathered in Nicaragua (where, as we said before, the virus survived under incredible conditions for several months) makes one reluctant to utter a categorical affirmation, even at this stage, as to a possible cessation of the epizoötic outburst.

A few special features of this episode should be pointed out, not simply for their historical interest but because of the conclusions which may be drawn from a series of facts peculiar to the ecology of the regions. These facts may throw a light on other epidemiological manifestations, not limited to Middle America and not restricted to the natural history of yellow fever. The features are related more especially to problems of transmission, extension and permanence of the virus and therefore come under two principal headings: Characteristics of the animal population, and characteristics and behaviour of the known and hypothetic vectors.

With regard to the animal populations involved it may be stated that never in our time, or in the time of our precursors, has a phenomenon of the intensity observed between 1949 and 1954 in Middle America been recorded. Two principal factors contributed to this. First was the fact of a universal susceptibility of the primate population (as suggested by the results of immunity surveys conducted west of the Panama Canal among sylvan humans). Secondly, there was the fact that the predominant species of this part of the world are extremely vulnerable to infection and non-resistant to it. A third

condition existed which certainly contributed to make the manifestations more dramatic and spectacular: the extraordinary density of the primate population in Middle America before the passage of the wave. One fact can give an idea of the numbers of those animals which could be found: preliminary immunity surveys conducted ahead of the wave allowed us to collect on several occasions over a hundred sera in five or six days (a record never attained in the forests of South America), and led us to the conclusion that these forests had not been visited by the virus for a very, very long time, in contrast to South America where the susceptible monkey populations are constantly whittled down by the enzoöty and are, therefore, reduced to scanty numbers of immune survivors.

To a large extent, these circumstances account for the massiveness, acuity and speed of the phenomenon; also, for its relatively short duration. It is well known that the proportion of insect vectors which become infected on a given animal is in direct relation to the titer of virus circulating in the infective host. It is further a well-known fact that highly susceptible animals such as the *Alouatta* and *Ateles* genuses multiply the infecting virus and carry it in high concentrations in their peripheral circulation for several days. A virus wave hitting any population of such animals has more chances to spread rapidly and extinguish itself for lack of fuel than if it had met another type of animal population, composed of less susceptible individuals, that is of less efficient infective hosts. This is important when we evaluate a given zone as to its endemic potentialities. The presence of animal species whose susceptibility is irregular and of low grade may be much more important from the standpoint of endemic permanence than the existence of populations of high susceptibility which can be instrumental in the outburst of spectacular manifestations, but which are not adequate to keep the menace latent for long periods—or forever. These remarks are not necessarily limited to yellow fever, but may well be extended to other infectious diseases.

Analogous considerations may apply to the vector problem. Theoretically, a highly efficient vector species may be defined as a species which, upon exposure to infection when biting an infected host, shows a high proportion of infection among the specimens exposed, with, consecutively, a short period of incubation for the transmitting ability to develop. Such a vector will have more probabilities to determine acute epidemiological or epizoötical accidents than a mediocre vector species, that is than one whose proportion of infection is lower and whose period of incubation is longer. Conversely, the mediocre vector is more liable to produce latent, prolonged, and occasionally ignored phenomena by killing or immunizing the susceptibles with slow tempo; and eventually, in the case of certain animal species, permitting their ranks to replenish before the process wears out. A combination of the ideal host with the most efficient vector is bound to provoke short-lived epidemic explosions. A combination of the mediocre host with the inefficient vector may well be the cause of prolonged endemic situations. It is not inconceivable that inter-

mediate conditions may arise, and one state evolve into the other. All this seems rather obvious; and yet what an ingrained tendency there is among researchers to ignore or give scant consideration to animal hosts or insect vectors when the results obtained from them by experiment or by observation in nature are not clear-cut and spectacular!

The Middle American yellow fever wave, for one, appears to have been the result of a perfect combination of efficiencies. At a certain moment, at a certain place, three factors coincided: first, the infective agent—the yellow fever virus—hitting the Panama Canal in one of its periodical excursions out of the big South American reservoir. Second, the vector; fluctuation studies in mosquito fauna which were being conducted at the time by workers of the Gorgas Memorial Laboratory show a peak instant in a record year. Third, a dense and highly susceptible population of primates. The fire caught, covered eight hundred miles in less than five years.

Concerning the identity of the vector or vectors of Middle America, it is not within the scope of this paper to enter into taxonomical discussions or entomological long-drawn considerations. But we should mention the fact that, of the known tropical sylvan yellow fever vectors, three exist west of the Panama Canal as far as the Costa Rica-Nicaraguan border: *Haemagogus spegazzinii falco, Haemagogus equinus,* and *Aëdes leucocelaenus.* The latter species disappears as one enters Nicaragua. As far north as the northern coast of Honduras and as far west as the Tela meridian (over 87° W.), the two former species persist. Then *Haemagogus spegazzinii* disappears, leaving *equinus* as sole representative of the tropical fauna. It is, I think, relevant here to mention a few facts concerning this interesting species. Its ability to transmit yellow fever by bite was demonstrated in Brazil under laboratory conditions. However, it has never been found infected in nature. In Colombia, at the experimental station of Volcanes, Caparrapi, it was found in small numbers in an infected area, together with *Haemagogus spegazzinii.* Several groups of the latter, ground up and inoculated intracerebrally into mice, showed a considerable amount of virus, whereas the *equinus* groups failed to show virus. A rhesus monkey bitten by over a thousand of these mosquitoes in a locality of Nicaragua where monkey mortality has been recently observed, did not show any sign of infection and failed to become immune. The fact that *Haemagogus equinus* is a universal mosquito which can be found at different altitudes, sometimes under severe and adverse conditions, had in the beginning led us to discard it as a potential vector, its universality being in disagreement with relatively localized manifestations. Then it was found, under laboratory conditions, that a great proportion of *equinus* do not have a life span compatible with the virus evolution, and die before the optimum incubation time is completed. All this seems to indicate that *Haemagogus equinus* may well be endowed with the characteristics which we ascribed to the theoretical "inefficient vector." I should like to add that this mosquito was present at the time and place where virus survived in Nicaragua

during the dry season of 1952-53. It is also present in Colombia, in some mysterious endemic areas where virus persists year after year, as shown by fatal human cases; areas of heavy human settlement where the simian population has been destroyed or reduced to such small proportions as to make it negligible as an epidemiological factor. Incidentally, those areas are densely populated by five genuses of semi-domestic marsupials; of these, four *(Metachirus, Didelphis, Caluromys, Marmosa)* have been experimentally shown to be susceptible to yellow fever and many of their specimens have been found immune in nature in endemic areas. Muzo, Caparrapi, and San Vicente de Chucuri, in Colombia, may well be instances of the "combination of inefficiencies" which we mentioned above.

Other possible vectors of the *Haemagogus* genus and of the Sabethine tribe exist throughout Middle America and should be mentioned here. In Costa Rica and Nicaragua, we have *Haemagogus mesodentatus, Haemagogus irridicolor* and *Haemagogus anastasionis.* As one progresses towards the North, *mesodentatus* persists, and new forms appear. They are new to science and are at this moment being studied under laboratory conditions at the Gorgas Memorial Laboratory. About their ability to transmit yellow fever we can only conjecture. But we are in possession of a few facts which are highly suggestive. They appertain to the history of sylvan yellow fever in ancient times, towards the end of the last century, and in the first years of this one. In his article "Anticipated Progress of Yellow Fever in Guatemala and Mexico, 1955-59," *American Journal of Public Health* (vol. 45, number 7, July 1955) Colonel Norman W. Elton states: "Not only was the Mayan Empire swept by sylvan yellow fever in 1484, as indicated by the epidemic of 'xekik' (bloody vomiting) to which reference is made in the Books of Chilam Balam of Chumayel and Chilam Balam of Tizimin, but this form of the disease has also been noted in northern Guatemala early in the 20th century." Sanchez reports credible accounts of the ominous silence in the forests of the Verapaces due to the annihilation of the howler monkeys by yellow fever in 1901, followed by a great epidemic in that same region in 1902. Gaitan records an outbreak of the sylvan form close to the Hondurian frontier in the Motagua Valley of the Department of Izabel, in the vicinity of Los Amates, in 1920.

One of the best accounts of the antiquity of yellow fever in Mexico is given by Connor who recognized areas of endemicity, such as Campeche, Tabasco, Veracruz, the Valley of the Papaloapan, Ticul, and the vicinity of Mérida. He noted the frequency of the disease among the population of the upland regions, such as the Oaxacan hills, only after migration to the lowland river fronts. These people, as related in the chronicles, were free from the disease until they visited the coastal areas to make war or engage in the harvest. Carter, rather skeptical because he did not believe yellow fever could exist in the absence of *Aëdes aegypti,* nevertheless comments on the periodic repopulation of the coastal areas by order of the Montezumas because of epidemics which at times wiped out the population of the lowlands. This was

primarily the "matlazahuatl," characterized by the vomiting of blood and other manifestations of a hemorrhagic diathesis, which was carried back even into the highlands.

The supposition of epidemics having occurred in 1901 and 1902 and prior to that is substantiated by the few positive sera found by Bustamante in 1942 in the upper Usamacinta among the 40-49 as well as over 50 age-groups. Moreover, we were able in one particular instance to gather first-hand and precise information from an old man (now living in Flores, Peten) about the occurrence of a heavy monkey mortality which coincided with a human epidemic in the Guatemalan Peten. This information was obtained when we were beginning to despair of getting anything but legends and contradictory second-hand rumors, after having systematically interviewed all the older persons in different localities. One of our guides told us of an 82-year-old man, Felix Castellanos, who used to evoke in the family circle a tragic episode of his childhood. This took place when he was ten years old (therefore around 1882). He had accompanied his father to a lumber camp established by a Guatemalan and Mexican concern at the mouth of the river Lacantun, where it falls into the Pasion river. Labour in those days was recruited in Tenosique, and the crews, with their families, were driven on foot across the big plain to Libertad, Sayaxché and to the Rio Pasion, under conditions very similar to slavery. Roughly one month after the arrival of one of these contingents, while the camp site was still being cleared, people began to die. They were seized by a terrible fever, vomited "black ground coffee" and in the following days became intensely yellow. This man lost his two brothers and a sister in that manner.

The camp was abandoned by most of the terrified survivors. One day the boy was alone, nursing his sick siblings, when through the door of the hut he noticed a band of howler monkeys, which usually came to a guanacaste tree (Higuronia) close to the camp. Suddenly he was amazed to see one of the monkeys drop to the ground. Soon after, another fell from the tree, and this continued to happen throughout the day; the monkeys hung on to the tree for a while, then dropped, or else they fell while trying to move on the limbs of the tree. When his father came back from the forest, in the evening, the boy told him what he had observed. "Of course," answered the lumberman, "this has been happening for some time in the forest. The whole place reeks with the stench of them."

The old man still has a vivid image of the dying monkeys, which, as he relates it, is associated in his mind with the death of his siblings and other companions. I was able to verify this last August when I succeeded in contacting Felix Castellanos, and I heard him repeat a description of the incidents consistent with the second-hand story previously recounted to us. He struck me as being in full possession of his faculties.

I have placed what might seem an exaggerated emphasis on the history

of the Peten for several motives. In the first place it is reasonable to assume that an epidemical occurrence, given similar ecological conditions, may repeat itself. Now this region, remarkable for its geographical isolation, has scarcely changed since 1882, with the exception of its recent contacts with the outer world by air. To the southeast, the destruction of forests and the intensification of cultivation in the Motagua and Ulua valleys may perhaps have rendered more difficult the invasion of a sylvan epizoötic coming from the South. However, the possibility of its happening is not excluded. A yellow fever invasion of the Peten should open singular possibilities. It would mean, in the first place, that the various *Haemagogus* species present in its forests are very probably efficient vectors of the disease. These species, including *Haemagogus equinus,* have a wide range of distribution in Mexico and Belize. Particularly, the range of *equinus* has been recently found by workers of the Gorgas Memorial Laboratory to include the region of Brownsville, Texas. The epidemical and epizoötical consequences are easily seen. Nor would this state of things be a mere temporary menace. It is fully conceivable that the system of forests existing in this vast area may well harbour latent and rampant infections over a relatively long period. Apart from monkeys, in the Peten we have the very genera of marsupials which are strongly suspected of playing a role in the permanence of yellow fever in certain areas of Colombia. It is true that up to now, and with the exception of a positive *Metachirus* serum obtained in an epizoötic area of Nicaragua, there has been no evidence that the Middle American invasion may have affected the marsupials. Nevertheless, since the program of studies which was undertaken by us did not include a thorough investigation of this problem, we cannot afford to discard possibilities of this kind.

Conditions exist, therefore, of such a nature as to transform the forests of Peten, Belize and Mexico into a potential reservoir of infection.

All these facts lead to one all-important conclusion: the yellow fever threat has not disappeared from this hemisphere. As long as virus will persist in the big South American reservoir, as long as there persists the possibility of its periodical irruption into adjacent areas—such as happened from 1949 to 1954 in Middle America—the danger is there of epidemic outbursts in communities which still present the veritable anachronism of harbouring *Aëdes aegypti.* The methods of control which followed Carlos Finlay's discovery reduced this danger to proportions which made life possible for urban populations where the awareness of the mosquito importance stimulated constant surveillance and where reduction of the indexes was maintained below a certain level. But the cessation of the dramatic episodes of the past produced as an understandable consequence a tendency to negligence in certain quarters. Permanent and rigorous measures of control in one place lose much of their efficiency when a neighbour is not as conscientious. Apart from that, any control which is based on indefinite routine procedures sooner or later is bound to slip; especially so in localities where public spirit has not attained the de-

sirably high level of development, and where adequate personnel cannot be found in sufficiently large numbers. Moreover, permanent control measures are a constant drain on Public Health budgets, and the surveillance which they entail can never relax, nor is it possible to contemplate its abandonment in the foreseeable future. Several urban epidemics which occurred in South America long after the Finlay doctrine was demonstrated provide ample confirmation of this assertion.

The means at our disposal today have opened a new chapter in the history of the fight against epidemical hazards. It is possible now to envisage more radical measures and to set more definite goals.

The results which have been made possible by the advent of the chemical age in the warfare against insect pests can confine forever the everlasting menace to its sylvan boundaries.

The eradication from the Americas of the urban vector of yellow fever can be viewed as the logical and ultimate consecration of Carlos Finlay's work. And it will constitute the most eloquent tribute to his memory.

EPIDEMIOLOGICAL NOTES IN CONNECTION WITH THE 1954 OUTBREAK OF YELLOW FEVER IN TRINIDAD, B.W.I.[1]

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Yellow fever was well known in Trinidad during the eighteenth and nineteenth centuries. The last urban outbreak occurred in Port-of-Spain in 1907 (Trinidad and Tobago, 1908). In 1914, the last reported cases of yellow fever for the island were reported among American oil workers at La Brea in southern Trinidad (Trinidad and Tobago, 1915). This group of people lived in screened bungalows in a zone where mosquito control measures were in force, but worked in the jungle. In retrospect, it seems probable that this latter epidemic represented an outbreak of jungle yellow fever, not transmitted by *Aëdes aegypti.* These early yellow fever accounts are reprinted in the *Caribbean Medical Journal,* Vol. 16 (1955), pp. 60-86.

Trinidad provided some early clues which might have helped in the solution of the riddle of jungle yellow fever, but which were apparently submerged in the medical literature for twenty years and more.

Charles Kingsley (1871), in his book *At Last: A Christmas in the West Indies,* makes the statement (p. 98) that the monkeys in Trinidad died, possibly of yellow fever "the year before last, sensibly diminishing their numbers near the towns." The year in question is probably 1869, when a yellow fever outbreak is recorded for Trinidad.

Balfour (1914) mentions dead monkeys in connection with the 1913-1914 Trinidad yellow fever outbreak near Brighton and La Brea, and speculates upon their connection with the disease.

These are thought to be the earliest known items concerning the possible role of monkeys in yellow fever epidemiology, and both episodes originated in Trinidad.

[1] The studies and observations on which this paper is based were conducted with the support and under the auspices of the Division of Medicine and Public Health of The Rockefeller Foundation, the Government of Trinidad and Tobago and the Colonial Development and Welfare Scheme.

Yellow fever was not recorded from Trinidad in official reports in the interval between 1914 and 1954. Personnel of the Trinidad Regional Virus Laboratory took many blood specimens in 1953 and early 1954 from Trinidad residents. These specimens were tested by the Rockefeller Foundation Virus Laboratories in New York, in neutralization tests employing several viruses in a general exploratory program.

Yellow fever neutralization tests were thus performed on 694 sera. In addition to a high percentage of immunes in older people, eight yellow fever immunes were encountered in young people between 15 and 20 years of age from east-central Trinidad. This challenging finding was reported to health department authorities and further exploration was planned. One hundred and fifty additional tests were run on children between 5 and 15 years of age from the same region and no positives were encountered.

Plans for further investigations were abruptly interrupted in April, 1954 by the finding of a yellow fever case. The virus was isolated from the blood of a young male forest worker from Cumaca, in northeastern Trinidad. This man was seen for mild undiagnosed fever in the Arima District Hospital (Anderson, Spence, and Downs, 1954). Following this, no further cases were seen until early in August. In August, September, and early October, 15 additional human cases were seen. Included in these were four fatal cases, of which one was diagnosed by pathological examination of a liver specimen and the others by isolation of virus from liver tissue after death, as well as by histopathological examination (Anderson and Wattley, 1955). In each of the 12 confirmed non-fatal cases seen, virus was isolated from the blood. In one instance the isolation was made on the twelfth day of disease (Downs, Anderson, and Spence, 1955).

Additional human cases were seen, diagnosis being dependent upon serological evidence only. Many of these cases are still being studied serologically. While exact numbers cannot be stated, it is apparent that the epidemic was much more extensive than anyone realized at the time. Indeed, there is enough evidence on hand to indicate that there were hundreds of cases of unrecognized yellow fever in Trinidad during 1954.

Following the finding of a human case, it was possible to determine that monkeys were dying in the forests. During July, August and September, 1954, six recently dead howler monkeys *(Alouatta seniculus insulanus* Elliott) were brought to the laboratory by hunters. These monkeys had been picked up dead or dying in the forests. A seventh monkey was received in January, 1955.

Two of these animals were quite badly decomposed, yet yellow fever virus was isolated from the livers of all seven (Anderson and Downs, 1955). Available evidence suggests that there was an extensive epizoötic in 1954 among howler monkeys of the island, killing off large numbers. Hunters also furnished two stories of dead, white face or capuchin monkeys *(Cebus apella*

Linn). No histories of dead monkeys prior to January, 1954, were elicited in questioning over a hundred hunters and woodsmen, except for two stories of dead animals seen about 1933, some two decades earlier.

Neutralization tests were performed on the sera of 73 monkeys shot expressly for such testing from various forested regions of the island. Nineteen of 61 *Alouatta* sera showed yellow fever neutralizing properties and 7 of 12 *Cebus* sera showed similar evidence of immunity. Whether this immunity represents infection in the remote or recent past has not yet been determined.

Extensive collecting of forest mosquitoes was carried out at Cumaca, Melajo Forest, and Charuma Forest. Mosquito suspensions were inoculated intracerebrally into weaned white mice. Yellow fever virus was isolated from 22 different pools of *Haemagogus* mosquitoes captured in the Melajo Forest and Charuma Forest areas and once from a mixed pool of 17 species of mosquitoes. The infected mosquitoes were in collections made in August and September. Most of the infected *Haemagogus* were collected at ground level rather than in trees (Downs, Aitken, and Anderson, 1955).

Aëdes aegypti inspections were made in houses of confirmed yellow fever cases as well as in houses of undiagnosed fever cases. In several instances where actual captures of mosquitoes were made, no virus was isolated from these mosquitoes.

At least three of the Trinidad human cases from which virus was isolated appear on epidemiological grounds to be *Aëdes aegypti* transmitted, one of these being from urban Port-of-Spain. The remaining cases were probably all forest acquired. Nevertheless, the occurrence of *Aëdes aegypti* in suitable breeding containers and in houses, not only in urban areas but also scattered widespread throughout the island, with indices in rural houses exceeding 70 per cent, makes it possible that some of the cases seen in forest workers and their families in rural areas may have been *Aëdes aegypti* transmitted cases.

To summarize, between April and October, 1954, yellow fever virus was recovered 6 times from *Alouatta* monkeys, 23 times from mosquitoes, and 15 times from human beings. With an additional monkey isolation in January, 1955, this is a total of 45 isolations of virus. Each strain isolated has been confirmed in specificity tests using known monkey serum from yellow fever immune animals.

Dr. Anderson, the virologist of the laboratory staff, had had considerable previous experience with yellow fever in Colombia, but for Dr. Aitken, the entomologist, and for Dr. Spence and myself, epidemiologists, this represented our first direct contact with yellow fever. It was particularly in the field of the diagnosis of yellow fever that we encountered our greatest difficulties and were tripped up quite smartly several times. Since the diagnosis of yellow fever is the first problem encountered by the medical and public health pro-

fessions, either in combatting an existing epidemic or in guarding a vulnerable frontier against introduction of the disease, the details of a couple of our blunders may serve to highlight the problem of diagnosis.

The so-called classical cases of yellow fever, with jaundice, albuminuria, bloody vomit, collapse, and death should offer no difficulties in diagnosis. Lest we be misled into thinking this to be so obvious as to require no further mention, it may be emphasized that none of the first three deaths in the Trinidad epidemic was initially diagnosed as yellow fever (Wattley, 1955) although clinicians in the hospitals had been alerted and although all of these cases were reasonably close to the classical picture. The fourth case was recognized as a yellow fever case before death. (While Wattley states that all these cases were forest acquired, we feel that the fourth case (Ba) described in detail below was probably an *Aëdes aegypti* infected case, infected in the home.)

Difficulties compound, however, with the milder cases, when jaundice is not evident. In a region where dengue, typhoid fever, and malaria are frequently seen, a patient complaining of fever, plus headache, backache, and aching joints attracts but little attention if he is only mildly or moderately ill. Our Trinidad laboratory staff has seen some 600 cases of fever, mostly falling in the mild undiagnosed fever group, before, during, and after the yellow fever outbreak. I am as yet unable to distinguish the mild yellow fever case from other common febrile illnesses on clinical grounds alone.

Following are examples from our clinical and epidemiological records.

On July 27, one of our laboratory technicians went to Charuma Forest acting on a story of dead monkeys related by some oil workers. He returned with a monkey skull with flesh still adhering, and brought with him an oil worker who had become ill with temperature of 102.5 the same day. Serum from this man infected mice and the virus was later proved to be yellow fever. While this was still but a presumptive lead, it was decided to establish a mosquito collecting station in the same forest. The same laboratory technician asked if he could borrow a truck on Sunday, August 8, to revisit the forest with a couple of other technicians. Permission was granted, the boys took the trip as a holiday outing, and we thought no more of it. On August 13, five days later, the same technician said his seven-year-old son had become ill on August 12 with fever and loss of appetite. It developed that the technician, unauthorized, had taken his unvaccinated boy (S.B.) with him on the August 8 excursion.

The boy was brought in. Aside from temperature of 104°, he did not look seriously ill. A blood specimen was taken and the boy was referred to the Colonial Hospital as a yellow fever suspect. Here we made our blunder: we sent him without a covering letter. The busy doctor at the admitting desk of the Colonial Hospital took a brief look at the boy, diagnosed tonsillitis,

and sent him home. The boy recovered uneventfully. We recovered yellow fever virus from the blood specimen. When the case was notified to the Health Department, an exhaustive search was made for secondary cases in the Port-of-Spain suburb in which the child lived. Houses surrounding this potential focus were sprayed with insecticide. No secondary cases were seen.

In retrospective study of this case, the father said the boy never left the roadside in the forested area where the truck was parked. And from another angle, during August and September, yellow fever virus was recovered 13 times from pools of ground captured *Haemagogus spegazzinii* from this immediate vicinity.

In this instance, although yellow fever was suspected, the boy, circulating virus, was permitted to return to a potentially *Aëdes aegypti* infested locale. We may have suspected yellow fever, but we really did not think it was a case. Because we lacked conviction, a public health blunder, fortunately a harmless one, resulted.

Another episode occurred at Brother's Road, near Tabaquite, in southern Trinidad.

A seven-year-old East Indian boy (Ba) fell ill on September 28 and died in the San Fernando hospital on September 30. Yellow fever virus was isolated from his liver.

We visited his home on October 6. It was located in a moderately heavily populated agricultural region, with cocoa, sugar cane, and rice under cultivation, and was some seven miles beeline from the yellow fever infected Charuma Forest.

By good fortune, an efficient public health nurse was at the boy's house the same day, and had a dozen members of the family and neighbors assembled on the front veranda. These people had heard the message broadcast from the sound truck which toured the country regions urging yellow fever immunization, but had not been sufficiently stirred to visit the immunization center, some three miles distant, when it was operating three weeks earlier.

The nurse had taken temperature readings on the assembled people and had two on hand with temperatures reading 99° F., and three more fever cases located in nearby homes.

The dead boy's father and brother were both forest workers in the Charuma Forest, so our attention was focused on them. The father denied any recent illness. The brother said he had had a slight fever about a month before his brother became ill. Blood specimens were taken on both of these men. Both specimens neutralized yellow fever virus. However, the father's serum was negative on complement fixation test with yellow fever antigen, indicating an infection in the more remote past, while the brother's serum

fixed complement in high titer, indicating an infection in the recent past. Thus evidence points toward the older brother's carrying a forest-acquired infection to his home, infecting *Aëdes aegypti* there, and in this way serving as the indirect cause of his brother's illness and death.

Two girls, aged 9 and 16, cousins of the dead boy, and living a quarter of a mile away, were on the front porch. The nurse indicated that both had temperature readings of 99°. The girls were examined cursorily. They did not know they had fever and had no complaints except for mild headache in one. Blood specimens were taken as routine. Both specimens yielded yellow fever virus. Later follow-ups established that both girls recovered rapidly and uneventfully.

We went up the road to the home of a small boy who was too ill to come to the gathering. I felt he was a yellow fever case, yet no virus was isolated and the later serological studies failed to support this diagnosis.

Next we visited the home of the dead boy's uncle and aunt, about half a mile away. Both were ill, the uncle prostrate with high fever and severe headache, the aunt less ill. Blood specimens were taken and the nurse was urged to get these people into the San Fernando hospital. They were taken there the next day and both recovered uneventfully. We recovered no virus from these two persons but, upon serological evidence, the seriously ill uncle did not have yellow fever and the less seriously ill aunt showed a strong conversion with both neutralization and complement fixation tests.

Dr. Aitken, the entomologist, found *Aëdes aegypti* breeding on the premises although no adults were found. We have belabored ourselves in retrospect for not searching the girls' house. Prospects there would appear to have been excellent for making an isolation of yellow fever virus from *Aëdes aegypti*. Excuses are that distances were long, the hour late, and the ice hamper already full of materials to get back to Port-of-Spain. The bare truth is, of course, that we did not really think those girls had yellow fever and did not attach enough importance to them.

The Brother's Road episode related above yielded the original yellow fever death, the probable source of infection, and three additional secondary cases, plus a lost opportunity of catching *Aëdes aegypti* actually at work. Such an opportunity may not offer itself again to yellow fever workers for another several decades, particularly with *Aëdes aegypti* eradication programs progressing so well in so many regions of the world.

The origin of the 1954 yellow fever outbreak in Trinidad is obscure. Maybe infection "hopped over" from nearby Venezuela, which is reported to have had cases in the Orinoco Delta region in 1953 and 1954. Or possibly the disease remains in Trinidad, smouldering, with occasional flare-ups.

The evolution of the 1954 yellow fever outbreak permits of interesting speculation. The Health Department of the Government of Trinidad and Tobago started an intensive anti-*Aëdes* campaign in June, 1954. This was a few days after indisputable laboratory confirmation of the first case seen in mid-April. An island-wide immunization program was begun in July, directed first toward forest dwellers. By the time the epidemic had reached its apparent peak, during August and September, 1954, a large proportion of the residents in the forested areas of the island had received immunizations with 17 D vaccine and extensive *Aëdes aegypti* control had been accomplished in the urban areas. Before the Health Department program was started, the island population in large part had never been immunized against yellow fever, except for the considerable immunization of older inhabitants as a result of earlier epidemics. *Aëdes aegypti* house indices were high, both in urban and rural areas. The stage was set for an explosive outbreak of yellow fever. Whether the Health Department's prompt and vigorous campaign headed off a serious epidemic will never be known. How many minor localized epidemics, such as the Brother's Road outbreak narrated above, may have been averted, is likewise an unknown story. Any one of these could have been the starting point for extensive, serious trouble. The fortuitous finding of the case in April, 1954, permitting a control program to be well under way before the epidemic peak was reached, may easily have served to prevent a major outbreak.

As is the case in most public health work today, credit for an intangible victory rests with many organizations, among them the Trinidad Regional Virus Laboratory and the Rockefeller Foundation Laboratories in New York for early recognition and later following of the epidemic; the Health Department of the Government of Trinidad and Tobago for prompt institution of control measures; and the Pan American Sanitary Bureau for immediate detailing of experts and for supplying large amounts of 17 D vaccine, the latter being sent from the Instituto Oswaldo Cruz in Rio de Janeiro and the Instituto de Estudios Especiales "Carlos Finlay" in Bogota.

SUMMARY

A brief history of the 1954 yellow fever outbreak in Trinidad, B.W.I., is presented. Special emphasis is laid upon difficulties in recognition of mild cases of yellow fever in the field. It is suggested that prompt recognition of the epidemic threat and early institution of control measures averted a serious epidemic.

References

Anderson, C. R., and Downs, W. G., 1955. The isolation of yellow fever virus from the livers of naturally infected red howler monkeys, *Am. J. Trop. Med. & Hyg., 4*:662-664.

Anderson, C. R., Spence, L., and Downs, W. G., 1954. Report of a case of yellow fever in Trinidad, B.W.I., *Carib. Med. Jour., 16*:68-70.

Anderson, C. R., and Wattley, G., 1955. The isolation of yellow fever virus from human liver obtained at autopsy, *Trans. Roy. Soc. Trop. Med. & Hyg., 49*:580-581.

Balfour, A., 1914. The wild monkey as a reservoir for the virus of yellow fever, *Lancet, 1:* 1176-1178.

Downs, W. G., Aitken, T. H. G., and Anderson, C. R., 1955. Activities of the Trinidad Regional Virus Laboratory in 1953 and 1954 with special reference to the yellow fever outbreak in Trinidad, B.W.I., *Am. J. Trop. Med. & Hyg., 4*(5):837-843.

Downs, W. G., Anderson, C. R., and Spence, L., 1955. Isolation of yellow fever virus from a human patient on the twelfth day of illness, *Trans. Roy. Soc. Trop. Med. & Hyg., 49:* 577-579.

Kingsley, C., 1871. *At Last: A Christmas in the West Indies,* Harper Bros., New York, ed. 1, p. 98.

Trinidad and Tobago, 1908. Medical. Annual Report of the Surgeon General for 1907-8. Council Paper No. 111 of 1908, pp. 4-5. Government Printing Office, Port-of-Spain.

Trinidad and Tobago, 1915. Report of the Surgeon General on the Medical Department for the year 1913-14. Council Paper No. 205 of 1914, pp. 8-9, 12-18. Government Printing Office, Port-of-Spain.

Wattley, G. H., 1955. Clinical aspects of 4 fatal cases of yellow fever in Trinidad in 1954, *Carib. Med. Jour., 17*:15-23.

THE UNFINISHED BUSINESS WITH YELLOW FEVER

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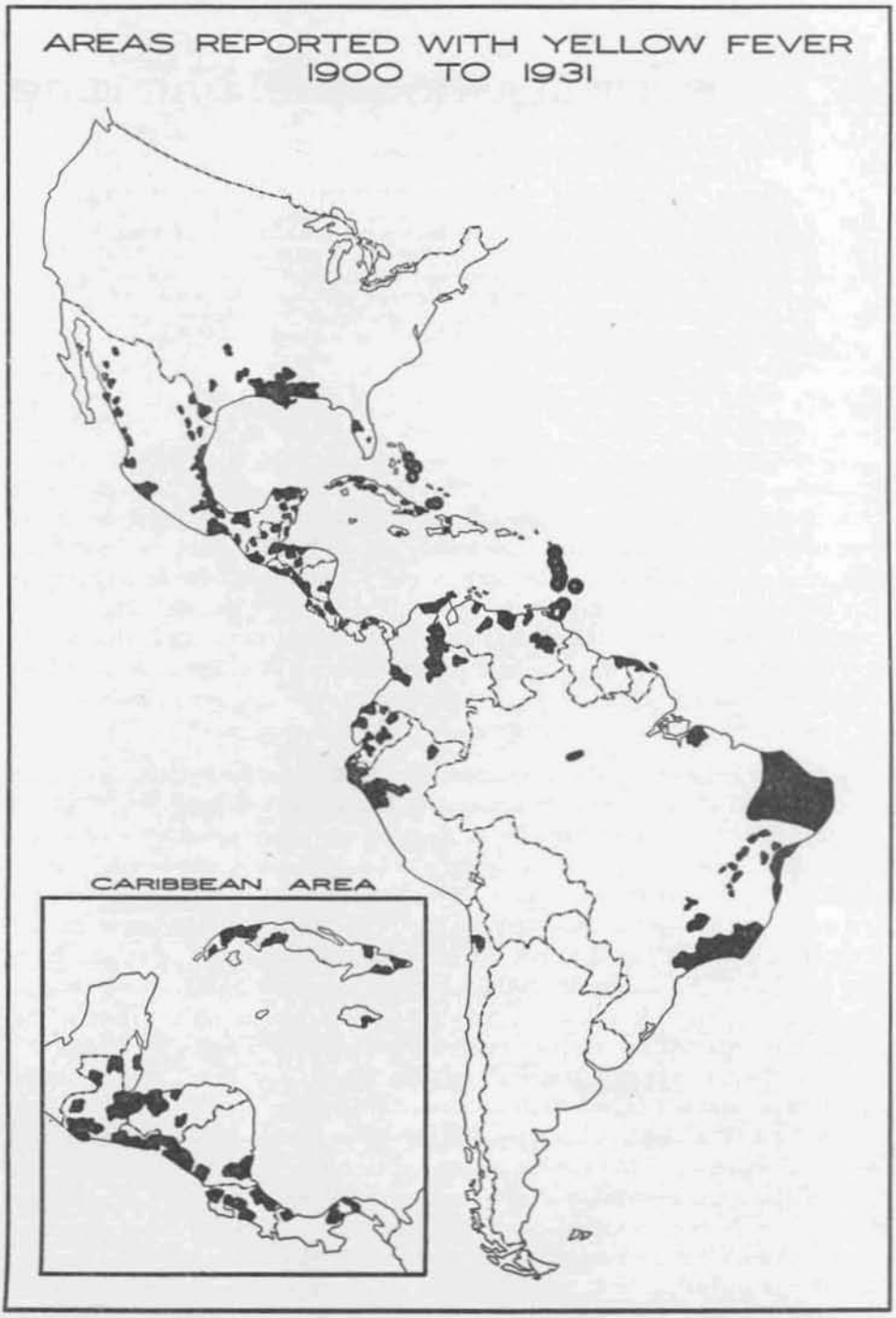
The contributors to this symposium, with an accumulated experience in the study and control of yellow fever of well over a century, are glorifying the victories over yellow fever since Carlos J. Finlay first expounded the theory of mosquito transmission. But during this year, 1955, fatal yellow fever cases have been reported from four American nations and from five to eight countries have reported outbreaks each year during the past decade. The experiences of Trinidad and of Central America already discussed show that a year or even a decade is not an adequate period of negative observation on which to discount the possibility of the reappearance of yellow fever, especially in the absence of careful, continuing epidemiological studies.

In Map 1 the areas of the Americas known to have had yellow fever during the period 1900 to 1931 are indicated. It must be assumed that all of the observed outbreaks reported during this period were *aegypti*-transmitted urban yellow fever, since jungle yellow fever was first definitely identified in 1932. It will be noted that reported yellow fever previous to 1932 was mostly coastal in its distribution and largely around the peripheries of South America and of the Caribbean. Map 2 shows the recognized distribution of yellow fever from 1932 to 1955, classified as urban *aegypti*-transmitted yellow fever and as jungle yellow fever. It will be noted that during this period the general distribution of yellow fever is more central than peripheral and that, except for a cluster of *aegypti*-transmitted outbreaks in North East Brazil, *aegypti*-transmission was reported only at isolated, individual points lying close to infected jungle areas. The cluster of *aegypti*-transmitted outbreaks in North East Brazil, together formed the last manifestation of endemic *aegypti*-transmitted yellow fever in the Americas which disappeared in 1934, following the organization of a rural *aegypti* eradication campaign. Had it not been for the existence of jungle yellow fever as a source of reinfection of cities and towns, the Gorgas-Rose dream of yellow fever eradication in the Americas would have come true two decades ago.


AREAS REPORTED WITH YELLOW FEVER
1900 TO 1931
CARIBBEAN AREA


AREAS REPORTED WITH YELLOW FEVER
1932 TO 1955
JUNGLE YELLOW FEVER
URBAN YELLOW FEVER

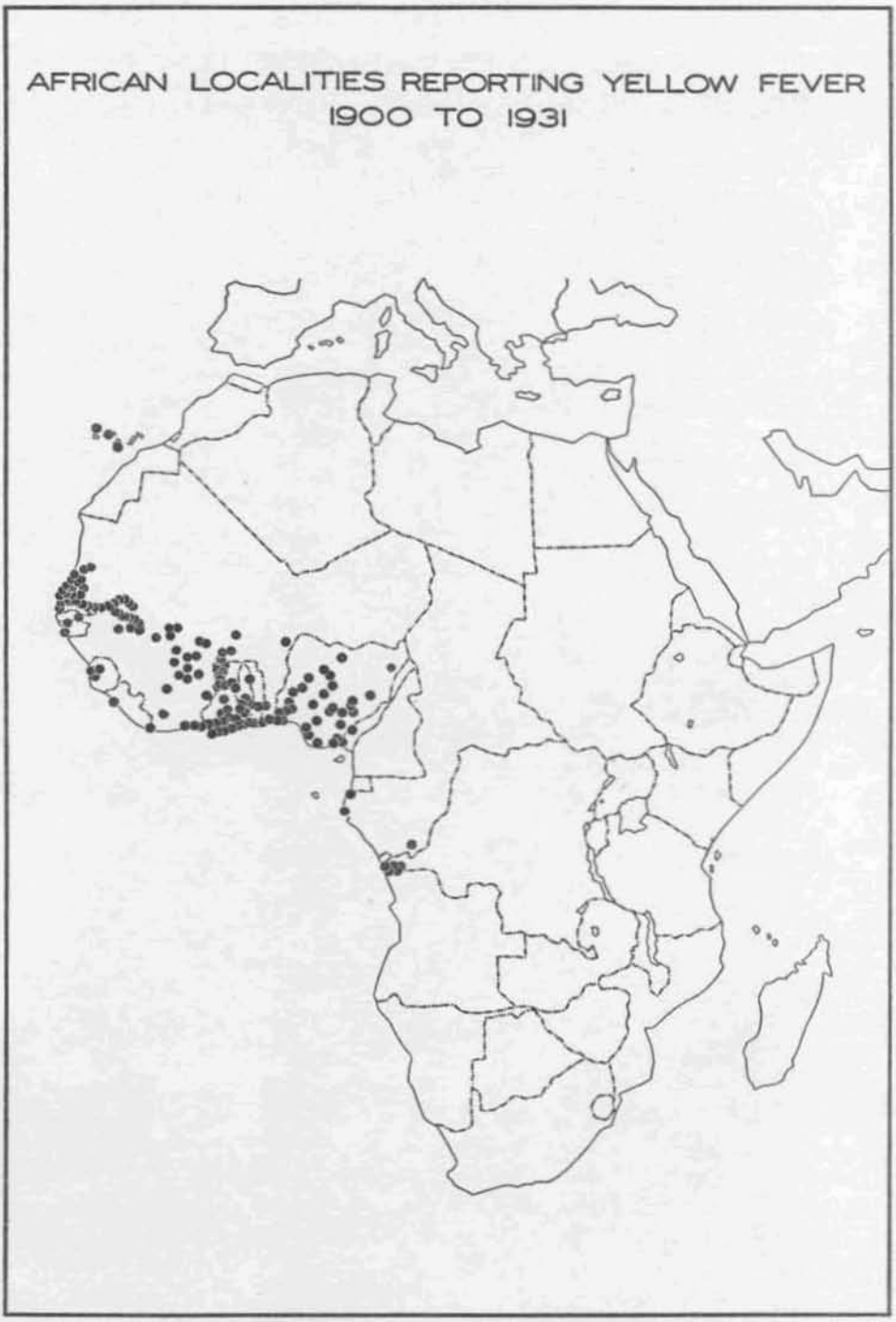
Special emphasis should be given to the scattered *aegypti* outbreaks shown, since *aegypti*-transmitted yellow fever always constitutes a threat to such towns and cities as still harbor this mosquito. *Aegypti*-transmitted yellow fever tends to spread along the routes of human travel, whereas jungle yellow fever generally moves from place to place independently of human passengers. When yellow fever comes to town, its danger is greatly increased, especially if the town be a travel center or a port city.

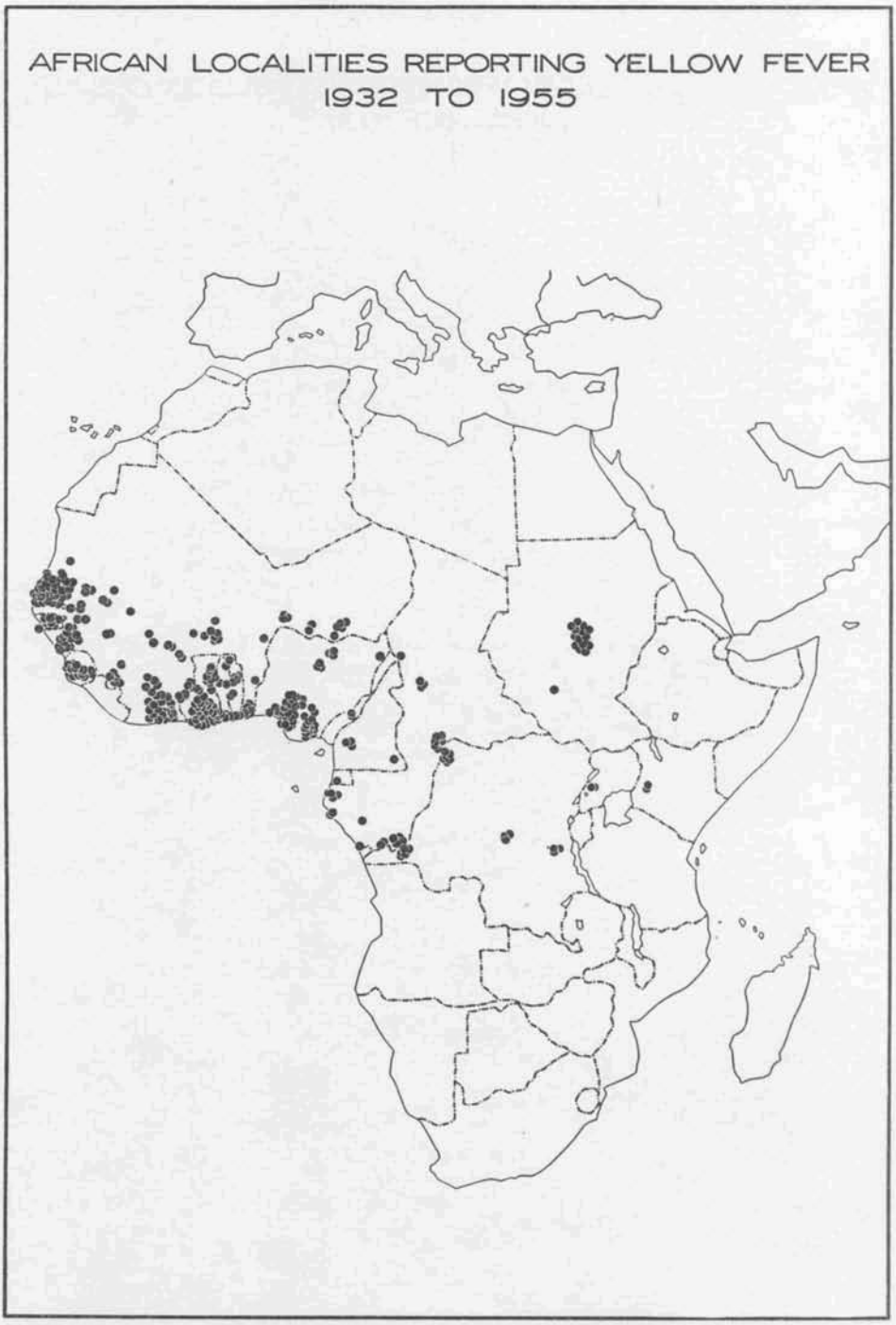
Only part of the yellow fever problem is in the Americas; Map 3 shows the reported occurrence of yellow fever in Africa from 1900 to 1931. It will be noted that this distribution is very limited and is essentially coastal — West coastal in fact. Map 4 shows the reported occurrence of yellow fever in Africa from 1932 to 1955. In Africa, as in America, the introduction of modern methods of study and diagnosis of yellow fever has opened up a whole continent-wide distribution of unrecognized yellow fever. I would point out that there is one basic difference in the information available from Africa and that in the Americas. In South America and in Central America there have been organized routine viscerotomy services for the collection of liver specimens from people dying after less than eleven days of illness, people who were not suspected of yellow fever, with the result that a great deal of otherwise silent yellow fever has been uncovered in the Americas, a type of yellow fever which is very seldom being diagnosed in Africa. The maps are not exactly comparable but the important thing is that the yellow fever area of Africa was much more extensive and continues to be much more extensive than was realized previous to the investigation on jungle yellow fever.

In Africa, as in the Americas, this widespread infection is a jungle infection in which man plays only a secondary role. Although there are differences in the jungle yellow fever of Africa and of the Americas, they are alike in that they were not recognized previous to the development of precision tools such as the neutralization test and viscerotomy for the certain diagnosis of past and actual present infections of yellow fever virus. Only in the general area of West Africa have *aegypti*-transmitted outbreaks occurred and to date yellow fever has never caused urban outbreaks in Central or East Africa, nor has it shown any tendency to spread to Asia.

In the Americas the early reports of jungle yellow fever were met with a great deal of skepticism. In an exchange of correspondence with Dr. C. E. Finlay some years ago, I said that I, better than most, could appreciate the difficulty his father had faced in convincing the world that yellow fever is transmitted by the *aegypti* mosquito because of the difficulty I had in convincing the same world that yellow fever is at times not transmitted by the same mosquito but transmitted by others.

Now that the existence of non-*aegypti* transmitted yellow fever is freely admitted by all, there continues great difficulty in getting recognition of the


AFRICAN LOCALITIES REPORTING YELLOW FEVER
1900 TO 1931


AFRICAN LOCALITIES REPORTING YELLOW FEVER
1932 TO 1955

fact that although jungle yellow fever is clinically, etiologically, pathologically and serologically indistinguishable from urban yellow fever, epidemiologically the two diseases are quite distinct and constitute entirely different problems from the standpoint of local prevention and international sanitary regulations. It is scarcely an exaggeration to say that urban and jungle yellow fever are as definitely distinct problems as are maritime-port plague and the so-called sylvatic plague of the Western United States.

The failure to recognize this difference between urban and jungle yellow fever is largely responsible for the persisting fear of the invasion of Asia by yellow fever, which has caused so much difficulty in recent years in getting full agreement on the WHO International Sanitary Regulations.

The fear of the possible invasion of Asia by yellow fever following the opening of the Panama Canal to interocean traffic in 1914, influenced the then newly incorporated Rockefeller Foundation to undertake the eradication of yellow fever in the Americas.

When, forty years ago this year, Wickliffe Rose, the first Director of the International Health Board, and William Gorgas, the Surgeon-General of the United States Army, joined hands in the program to eradicate yellow fever from the Americas, a new concept in international health was born. This concept calls for the coordination of the measures against a communicable disease wherever it may occur in a region until the seedbeds of infection have been eliminated and the infective agent itself has disappeared for the benefit not only of the infected and uninfected countries of the region but also for the protection of exposed regions which may lie on the other side of the world.

The eradication concept which was developed to meet the situation created by improvement of steamship movement from the Atlantic to the Pacific through the Panama Canal, is much more important in relation to the development of rapid air travel than it is in relation to shipping. More and more emphasis will be given to the solution of most international health problems at their source as time goes by.

The discovery of jungle yellow fever as a source of reinfection of cities with yellow fever virus dissipated the dream of eradicating yellow fever as an infection but the eradication concept remained. With the demonstration, in 1933, that the urban and maritime vector of yellow fever, the *Aëdes aegypti* mosquito, can be eradicated, there began the development of nation-wide campaigns for the eradication of this vector in various countries of South America. The initial skepticism with which reports of the species eradication of *aegypti* was received, was largely dispelled by the dramatic eradication of *Anopheles gambiae* from North East Brazil in 1939-40 and species-eradication became a respectable term in public health circles.

The eradication concept has forced the public health worker to reorient the evaluation of his success in handling preventable disease. Once he admits

that a disease is preventable and takes credit for such reduction as may have occurred from previously higher levels, he must be ready to explain the remaining incidence and the failure to bring that incidence down to zero.

In the light of the eradication concept, let us look at what unfinished business remains before the cities and towns of the Americas are guaranteed against invasion by yellow fever, before rural and jungle populations are protected, and before all danger of spread to presently noninfected areas of the world has disappeared.

The unfinished business of protecting permanently all cities and towns and certain limited rural areas in Brazil, Colombia and Mexico can be accomplished by completing the present program for the eradication of the *Aëdes aegypti* mosquito in the Americas. Already well advanced or terminated in most countries, the campaign for the eradication of *aegypti* can be said to have only begun in Argentina and Mexico and to have been very largely ignored in the United States.

The United States is practically alone in its failure to initiate *aegypti* eradication. This country is fairly well protected by eradication of *aegypti* in cities close to jungle yellow fever areas but this protection will disappear should these cities be reinfested with *aegypti* from the United States itself.

Not only is the United States threatening its own future but is failing to live up to the first application of the eradication concept on a regional basis. And this concept will surely be of tremendous interest to the United States in getting the collaboration of other countries in handling other health problems on a regional or world-wide basis in the future.

I cannot forbear quoting from the Annual Report of the Surgeon-General of the Marine Hospital Service of the U. S., as the USPHS was then known, for 1895.

The coast of Florida was patrolled by four revenue cutters carrying medical sanitary inspectors of the Marine Hospital Service to intercept fishing smacks which traveled down the coast of Florida, coming direct from Cuba, with no intent of entering legally any port of entry, but with the intent of smuggling, and also for the purpose of intercepting any returning filibustering expeditions or refugees from the island of Cuba seeking to land surreptitiously. Medical inspectors were stationed permanently in Havana, Santiago, and inspectors were also sent to every seaport of Cuba to make reports to the Bureau on the prevalence of yellow fever therein. Special inspections were made of the South Atlantic and the Gulf quarantine stations. All possible defects in administration or appliances were corrected and the whole corps of quarantine officers of this portion of the United States were made to feel the necessity of extra vigilence. Fortunately, no case of yellow fever landed upon the coast. In Cuba today there is a very active program for the eradication of

the *Aëdes aegypti* mosquito from the island and, I imagine that, if the lack of activity continues in the United States, the Director of National Health Services of Cuba might very well, a few years hence, report on similar activities on behalf of the Cuban Government patrolling the waters between the United States and Cuba to prevent the reinfestation of the island by the mosquito which has ben so expensively eradicated from that island.

I now turn to page 428 of the same report from 1895, and I quote: "In closing . . . my report relating to yellow fever, it remains to be said that immunity to this dread pestilence will only be secured by intelligent sanitary work in our Southern seaports . . .; and also by demanding of our neighbors that their ports shall be made to be as of little danger to the people of the United States as the ports of this nation are to them."

Again I suggest that the shoe is on the other foot. Our Latin American neighbors have gone so far ahead of the United States in this particular program that I, as an American citizen, and as Director of the Pan American Sanitary Bureau, am repeatedly embarrassed when my Latin-American friends say to me, "Yes, yes, we're doing this, we're doing what the Bureau is insisting, but what is your country doing?", and I have to say, "Well, just give them time, just give them time." But the years go on. It is eight years now that we have been on this continental program and nothing happens.

I would repeat what I said a moment ago, that in the past decade jungle yellow fever has been reported in from five to eight of the following countries—Argentina, Brazil, British Guiana, Bolivia, Colombia, Costa Rica, Ecuador, Honduras, Nicaragua, Panama, Peru, Trinidad and Venezuela. All of these countries are within one day's flight by plane and many of them within a few hours.

I would call attention to the fact that, in 1954, for the first time in 25 years, a maritime port in the Americas was infected with *aegypti*-transmitted yellow fever.

I would repeat again the fact that was already mentioned here, that in 1954 an infectious case of yellow fever did for the first time travel by air. It is true the flight was a national flight, but it traveled the distance of 200 miles and took an infectious case of yellow fever into the city of Caracas which had at the time a fairly high *aegypti* index, a city where yellow fever had not been recognized for four years.

It is difficult to believe that the people of the United States who have recently shown their interest in individual health in the financing of the polio vaccination programs, which is based on the reports of vaccinating 100,000 children for the prevention of thirty or forty cases in a year—I repeat I do not believe that the people of the United States, who have faced up to the costs of preventing poliomyelitis at the cost that has been indicated, desire to have it

said that this country cannot and will not spend the money to eradicate a mosquito which, by remaining in the United States, creates a threat to the reinfestation of neighboring countries which have or are eradicating it as part of a continental program to guarantee the Americas forever against urban yellow fever. This program is, for the United States, the most important unfinished business in regard to yellow fever and only from this can the United States and the rest of the Americas get the full benefit of the genius of Carlos Finlay and all of the work which has gone into the last half century.

THE GLORY OF THE UNITED EFFORT IN A GREAT CRUSADE

DR. JOSEPH E. SMADEL

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In the story of man's triumphs over his own infirmities no chapter stands out more brilliantly than that of yellow fever. Not only has this conquest been great enough to alter much of the world's history and its economic patterns, but the results have been so brilliant as to light paths for the solution of many other problems. This history of yellow fever is a success story and in it may be found much to aid us in our attempts to solve our current problems.

Others at these ceremonies have eulogized individuals and indicated the steps toward ultimate success which resulted from their deeds. This is fitting, and I am delighted that my predecessors on this program have recounted the keen observations and bold thinking of Finlay, the brave and meticulous efforts of the Reed group and the astonishingly successful vector control measures of Gorgas and his associates. Furthermore, men of the Rockefeller Foundation who took an active part in the unfolding of the yellow fever story have mentioned the countless contributions of their group to an understanding of the virology, epidemiology, ecology and immunology of this disease.

I wish to speak first about certain of the factors that aided these investigators in accomplishing their individual tasks and later mention other factors which contributed to the united effort. The popular notion is that any problem can be solved, given means, manpower and opportunity. Like most generalities there is some basis of truth in this notion. Certainly these necessary elements are to be found in the record of the conquest of yellow fever, but the important question is, how were they attained? Who provided the means, who enlisted the men with the required interest and ability and who created the opportunities or capitalized on the intangible ingredient which might be labeled "good fortune"? Let us see if we can find answers to some of these questions.

In the present age we often regard public demand as being of importance in initiating and sustaining interest of investigators in a given disease. Mere mention of poliomyelitis, cancer, heart disease and cerebral palsy will acquaint

you with the kind of public clamor, stimulated or natural, that I have in mind. Such public demand would seem to have been of little importance in the conquest of yellow fever.

During the summer of 1853, which was the year Carlos Finlay enrolled at the Jefferson Medical College, there were 128 deaths from yellow fever in Philadelphia and almost 8,000 in New Orleans. Except where yellow fever invaded new territory, or returned after a long absence in severe epidemic form, it was usually accepted as an act of God by the lay population, that is, it was regarded in much the same fashion that we now tolerate the shameful number of casualties which result each year from motor-car accidents or the high incidence of tuberculosis in some sections of the country.

If not public demand, then what did provide the drive for the continuing intensive study of yellow fever for the three-quarters of a century since the dawn of the microbial era? I believe it was provided in large part by the deep humanitarian and scientific interests of a relatively small number of men. Carlos Finlay, who stood alone for so many years, was one of these. George M. Sternberg was another; he was a friend of Finlay, a member of the Havana Yellow Fever Commission in 1879, an investigator of yellow fever for almost two decades; he was the first prominent bacteriologist in North America and was Surgeon General of the United States Army from 1893 to 1902.

Sternberg's sustained interest in, and vigorous support of, work on yellow fever made possible the successes of Reed in Cuba. Subsequently, General William C. Gorgas and General Frederick F. Russell provided the leadership and continuity for the attack on this disease. Thus, interest, support and continuity of leadership, all essential ingredients in any protracted campaign, were maintained for almost three decades by the Army. Thereafter, these three essential ingredients were provided by the Rockefeller Foundation, first in 1916 with the appointment of Surgeon General Gorgas as Director of the Rockefeller Foundation Yellow Fever Commission and later by General Russell who assumed the directorship of the International Health Division of the Foundation. Following General Russell, Dr. Wilbur S. Sawyer and Dr. George K. Strode served as Directors of the International Health Division. Hence, in the period of a little more than half a century, command of the major forces aligned against yellow fever passed through the hands of five outstanding scientists, each of whom had been prepared for the great task by many years of work in the field and in the laboratory on yellow fever.

Each of these leaders had the prestige to attract the right men to their organizations and the capacity to stimulate them to perform great deeds. Each knew the value of basic science and throughout this long period none hesitated to devote an appreciable portion of the available facilities to the establishment of a fundamental point of fact, when such was crucial to further progress toward the control of yellow fever. These men were excellent ad-

ministrators. I suspect that their greatest contributions to medicine and health were probably made during their more mature years when they devoted themselves to leading the general attack.

In emphasizing the importance of the five directors I would not neglect the impersonal organizations of which they were members. The Army Medical Service and the Rockefeller Foundation have great and unique potentialities for providing means, manpower and opportunity for medical research. These potentialities were exploited to the utmost in the battle against yellow fever. The accomplishments of the Army stand to its everlasting credit while the sustained effort of the Rockefeller Foundation ranks as the greatest monument in philanthropy.

While we are speaking of the elements of success in the war against yellow fever and the role of organizations in attaining these, I wish to digress for a moment and consider the future. The Rockefeller Foundation, after leading the battle for over a quarter century has indicated its intention of withdrawing from the field. The means for controlling yellow fever are at hand, but the wishful thinking of four decades ago that this disease could be eradicated from the Americas has proved unfounded. We and the generations to come are faced with a continuing guerilla action against the jungle cycle of yellow fever virus. We cannot hope to win decisively by eliminating the virus. However, by applying what we have learned we can maintain supremacy by confining the virus to its wilderness reservoirs. Let us hope that we and those who follow have the wisdom and vigilance to keep the virus at bay in the jungle and to keep our cities and trade routes free of the urban vector.

If the Rockefeller Foundation will no longer lead us, then who will assume this responsibility and provide the Americas with the intelligent and resolute leadership required for the continual surveillance, the police actions, and the occasional beachhead landings, against yellow fever? The problem of maintaining control over this disease is an inter-American one since it affects, or threatens, each nation in the hemisphere. The Pan American Sanitary Bureau has already stepped into the breach. Yesterday you heard Dr. Soper and others recount the results of the most recent skirmishes in the continuing war on yellow fever. What group could be better suited to guide us in the future in our joint efforts than the Pan American Sanitary Bureau?

To return to certain of the ingredients of success in the conquest of yellow fever, one of these was the close integration of field work and highly technical laboratory investigations which could be performed only in a base installation. The principle of rapid and effective interchange of information and personnel in the field and laboratory was begun with the Reed Board. The Army Medical School, on whose staff Reed served as the Professor of Bacteriology, provided the base laboratory for the Cuban work. Experiments were performed at the School which led up to the investigations in the field.

Furthermore, members of the Board returned to the School to complete their work. During the many years that the Rockefeller Foundation led the battle against yellow fever, its International Health Division Laboratory in New York served the field units in a manner similar to that by which the School had served the Reed Board. In the laboratory in New York was done the fundamental work on developing serologic diagnostic procedures, methods for immunization against the disease and basic work on the nature of the virus of yellow fever. Each of these studies on yellow fever uncovered new principles and provided background knowledge which has been of importance in the general field of virology. The base laboratory also provided an important cohesive force for the development and maintenance of esprit de corps in a far-flung operation which continued over many years. It provided the opportunity for sound scientific training of recruits and permitted the field worker to return to a well-equipped workbench to test the hypotheses which he had developed in the jungle. Finally, it enabled the group to develop and use complicated technical procedures which could not be employed in the ordinary virus laboratory or in the field laboratory. Perhaps I have spent too much time in discussing the role of the base laboratory in the ultimate success; however, in my opinion this is one of the important lessons which we should have learned. In my own work I repeatedly see the value of free interchange between the field and the supporting laboratory. Without this, the former rapidly degenerates into the unimaginative practice of therapeutic or preventive medicine and the latter devotes itself to an ivory tower type of research too far removed from the ills of mankind.

A unique and important ingredient in the early studies on yellow fever was the development of the concept of the use of lay volunteers in medical research dealing with problems in which crucial information could be obtained by no other means. The famous physicians of history who experimented on themselves and by so doing had made significant scientific contributions do not belong in the category of lay volunteers. Finlay employed over a hundred Spanish soldiers and Jesuit priests in his attempts to immunize against yellow fever by permitting mosquitoes, presumably infected with a mild strain of the agent, to feed on the men. These were bold experiments and demanded bravery in the volunteers. However, the volunteers were persons who were faced with the likelihood of contracting yellow fever in the normal course of existence in Cuba. Hence, the possibility of acquiring a mild attack, which would immunize against the natural disease, provided some personal incentive to these volunteers.

In contrast, the volunteers of the Reed Board had the promise of a severe and perhaps lethal disease and any immunity which might result from the experience was of little importance to most of them. Thus, these individuals exemplify for the first time the layman with such selfless devotion to mankind that he voluntarily jeopardizes his life in the hope of preventing or diminishing the ailments of other human beings. While by no means the

prerogative of the Americas the role of human volunteers has been greater in American medicine than in that of other areas. I have often wondered why. Is the urge to volunteer part of the generosity and community participation that characterizes the pioneers of young nations? Is it some peculiar interpretation we apply to our religious doctrines in this age which corresponds with that which motivated the crusades? Or is it as one of my friends said recently merely part of our national neurosis for health? Whatever the motivation that impels such volunteers to risk their lives without hope of personal gain, I wish to pay it homage. When we speak of the glory of the effort in yellow fever we speak in part of these men. I cannot leave this subject without commenting on the attitude of so many of my European colleagues on the participation of volunteers in medical research. Some, with justifiable revulsion against the Nazi crimes, oppose the use of volunteers under any circumstances. Others have difficulty in believing that the volunteers are fully informed and truly participate of their own desire and volition. The solicitation of volunteers for medical research is to be undertaken now with as much caution and reverence as displayed by Reed. Indeed the principles used by the Reed Board for employment of volunteers in the work on yellow fever have been incorporated into the accepted conventions of American medicine for accepting volunteers for participation in medical research. (Reference: J.A.M.A., 1946, 132, 1090.)

The Walter Reed Board and its success formed the spiritual pattern for the Army Commissions of both world wars, and for the present system of Commissions and their field teams responsible to the central Armed Forces Epidemiological Board. Unfortunately, even the medical public is not too familiar with this system of combined civilian and military enterprise, nor is it entirely familiar with the complexity of the medical research program supported by the Armed Forces. In the field of infectious diseases alone, one may point to achievements of the Armed Forces Commissions in the past 15 years in influenza, encephalitis, dengue, typhoid fever, the rickettsial diseases, plague, hemorrhagic fever, hepatitis, leptospirosis, streptococcal diseases, the dysenteries, and many others.

A number of ingredients which contributed to success have been mentioned. These were: means, men and opportunity provided by two great organizations; a succession of far-sighted scientific directors who made yellow fever their life's work; the close integration of practical field studies with basic scientific research in the laboratory; the employment of volunteers and the use of the commission system. But what of the most important ingredient of all — the men who actually did the work in the field and in the laboratory. These men did not merely contribute to success — they made success. They have been of no particular race or nationality or religious belief. Some have been loud, some shy, some brilliant, some stupid. But once involved in the study of this disease they amalgamated to form an ardent brotherhood of purpose. In almost all instances they have been highly trained men, attracted by

the vastness of the ignorance. They were adventurers in technical and intellectual skills. One almost senses that these people were born for high adventure.

It is the popular practice to single out certain individuals for credit in any success story. Frequently these individuals are made the objects of homage and adulation. But the story of yellow fever is one of many men. Who can deny the importance to the end result of the men who volunteered their lives, of the technical corps whose work was indispensable, of nurses who cared for the sick, or even of the men who cleaned the floors? This was indeed an inspired brotherhood, each individual a vital part of progress. In most instances the individuals had that feeling of pride which goes with being a part of a great spiritual enterprise. The relationships were so close and the rivalry so slight that it is almost impossible to trace the origin of many developments.

Reed, Gorgas, Lazear, Carroll, Agramonte, Mahaffy, Stokes, Bauer, Theiler, Soper. What names these are! They typify the modern odyssey. Carlos Finlay has full seniority amongst the officers and a place of immortal affection in the minds and hearts of all members of the crew, for he it was who furnished the one indispensable ingredient of success. He had the prime idea.

MEMORIAL ADDRESS — CARLOS JUAN FINLAY, CLASS OF 1855

DR. ALEXANDER J. ORENSTEIN

Honorary Fellow Royal Society of Medicine, Fellow Royal Society Tropical Medicine and Hygiene (Hon.); LL.D. (Hon.); C.B.; C.M.G.; C.B.E.; Chief Medical Officer, Rand Mines Central Mining Corporation (Johannesburg); formerly Director General Medical Services, Union of South Africa Defense Forces (World War II); formerly Director of Medical Services (East Africa); formerly Acting Director, South African Medical Corps (World War I); formerly Panama Canal Medical Services (1905-1912). Pre-eminent in the field of industrial medicine. He has applied the theories of Gorgas to secure the welfare of vast numbers of men employed in mining operations.

First of all, I must express my sincere gratitude to the authorities of my Alma Mater for the honour and privilege of participating in this notable occasion. I pray your indulgence if I fall below your expectations. In the words of Daniel Everett, I beg you —

"Don't view me with a critic's eye,
But pass my imperfections by."

There is one thing I can promise you: I shall not forget the injunction of Ecclesiasticus: "Let thy speech be short, comprehending much in few words."

The purpose of this meeting is to honour the memory of a distinguished son of Jefferson, Carlos Juan Finlay, or as he signed official correspondence in his capacity as Chairman of the Havana Yellow Fever Commission — Charles Finlay.

We honour the memory of Finlay because by his prophetic vision and by his persistence he inaugurated a new and tremendously important phase in the never-ending struggle of man against the ravages of disease.

I must justify the use of the strong expression "tremendously important." It may be hard for most of my hearers to realize how very important urban yellow fever was in Finlay's time, and before his time. Here are just a few instances of what it has done in this country alone; and it must be remembered that the disease also broke out in epidemic form many times in South American cities, in Cuba, and elsewhere. In the 18th century the then three principal ports in this country were attacked with tragic consequences. There are records of some 41,000 deaths in New Orleans, 10,000 in Philadelphia and 3,400 in New York. In the 19th century it is estimated that there were 100,000

deaths from the disease in the United States. The financial losses due to quarantine measures are estimated at about a hundred million dollars in the one year, 1878. At present purchasing power of money that would be about five hundred millions.

The psychological effect of an outbreak of urban yellow fever was overwhelming. The life of the affected community was profoundly disorganized and fear stalked the streets. It is within my own experience that workmen from the States left Panama on the same ship on which they arrived when they saw funerals and were told it was "yellow jack." There was an amusing incident concerning a member of a Congressional Committee, originally of seven members, on a visit to Panama. Six only arrived and were met by the then Quarantine Officer, the late Major La Garde. A load of coffins were being unloaded from the ship, among these six grand metal caskets. One of the Commissioners asked La Garde for whom these special coffins were intended. La Garde's answer—"Mr. Burr didn't come down, you know"—sent the enquirer post-haste back on board.

Indeed, at one stage, when yellow fever broke out in Panama City, Colon and few other places, twenty-two of these in the Headquarters building, there was a rush to get away which seriously threatened the work on the Canal.

It is merely a statement of fact to say that the Panama Canal could not have been built if yellow fever had not been eradicated.

It is against this background that the importance of Finlay's advocacy of the mosquito transmission of yellow fever must be judged.

Finlay was born on December 3rd, 1833, in Camaguey, Cuba. A loyal and devoted Cuban, he was not of Spanish blood but the son of a Scotch father and French mother. His father was a doctor, educated in Edinburgh and France. Carlos Finlay was educated partly in Cuba and partly in France, where he was sent at the age of eleven in 1844 to live with a relative. There he developed chorea, which left him with a lasting slight impediment in enunciation. He returned to Cuba in 1846. In 1848 he went to France again with his family, but the revolution was on and they went to Germany, where Finlay was at school for a year. Later he returned to France, where he entered the Lycee at Rouen. He thus acquired a good knowledge of three languages, French, English and German, in addition to Spanish. It is recorded by his son that he also read easily Latin and Greek, and was a good mathematician and physicist. His intention was to study medicine in France, but an attack of typhoid caused him to return to Cuba. After recuperating, he went with his uncle to study medicine at Jefferson, where his preceptor was John Kearsley Mitchell, father of S. Weir Mitchell.

It is fascinating to recall, however briefly, what Jefferson was like when Finlay was a student. Professor Goodner, to whom and whose secretary I am indebted for much factual material in this discourse, tells me that the faculty

consisted of seven: Dungleson, Huston, Bache, Pancost, Mitchell, Mutter and Meigs. The last three were well remembered in my time—I wonder, are they now? The course of study was supposed to be three years, but only two of these had to be spent at Jefferson, at a total cost of $35! At the end of the course a thesis had to be presented.

In Finlay's time here there were 31 States in the Union. The population was about 30 millions, of whom some 3 millions were slaves. The army had the imposing strength of some 11 thousand, all ranks.

In 1855 bacteriology was undreamed of: Pasteur was still working on crystals. Robert Koch was a boy of 12. Lister was a dresser in University College Hospital, London. Walter Reed a child of 4, William Crawford Gorgas an infant.

In our profession, opening of the abdomen was a deadly hazard. Surgeons prided themselves on their dexterity and speed, and could and did do amputations and cataract operations in the same morning session, working in their old frock coats, often well decorated with pus and blood. Anaesthesia with ether and chloroform was less than a decade old, and not yet whole-heartedly accepted. There were no X-ray machines, no cardiographs, no sphygmomanometers, none of the many gadgets some now have to cart about when they go on their rounds. There were no laboratories and clinical pathologists to bless or damn, according to whether their reports helped or bedevilled.

Specialism, the modern development which threatens to divide our profession into isolated horizontal layers, was unknown. It was still possible for the average doctor to compass all the knowledge and skill he required to serve the community reasonably well and with an untroubled conscience.

Such was Finlay's world when one of a class of 257 he received his diploma of Doctor of Medicine from Jefferson on March 10, 1855.

Although he was advised by Mitchell and others to practice in New York, he decided to return to his native land. In 1857 he passed the examination of the Havana University, a necessary step to enable one to practice medicine in Cuba, and started in general practice and ophthalmology. In 1860-1861 he went to Paris and attended clinics in general medicine and also eye disease.

He married in 1865 Miss Adele Shine, born in Trinidad, both of whose parents were Irish, and who was a most accomplished lady.

Finlay led a busy professional life, playing a full part in the cholera epidemic in 1867-1868. He however found time for research, no easy matter in days when there were no laboratories to which he could turn for help. He also wrote on many subjects, such as leprosy, beriberi, cholera and relapsing fever. His great asset was determination — once he started on a subject, he pursued it despite all obstacles put in his way.

His first connection with yellow fever was in 1879, when he was appointed by the Cuban Governor-General to cooperate with a United States Commission sent to Cuba to study yellow fever. His work with this Commission appears to have influenced him to the belief that there is an intermediary factor in the transmission of the disease and that this factor is a mosquito.

He is described by those who knew him as a man of exceptional charm. Mrs. Gorgas writes that he was the "perfect type of the beloved physician . . . who combined in his own person a keen mentality, a tireless persistence and the utmost geniality and graciousness of manner." Gorgas writes —

> "A most lovable man in character and personality; no one could be thrown with Dr. Finlay daily as I was for several years without becoming warmly attached to him and forming the highest estimate of his scientific honesty and straightforwardness. Being familiar with yellow fever both historically and clinically, I was constantly bringing to his notice instances in the past which could not be accounted for on the mosquito theory. Dr. Finlay, with the greatest ingenuity, was able to explain how the mosquito theory could be turned so as to meet just such contentions. I remained unconvinced."

A contemporary portrait supports this appraisal. At the time of the Spanish-American War he was about 65 years old, yet he went to Washington, offered his services to the American Army and served in the Santiago campaign.

Here is another bit from Mrs. Gorgas' recollection of Finlay —

> "Dr. Finlay was a well-rounded citizen and physician; he was a scholar, too, in other fields, with a fine taste in old Latin manuscripts, and something of an authority in heraldic and historic studies. But it was his amiability of character that had for so long endeared him to the people of Havana. His kindly face, adorned with side whiskers, and surmounted by a large crop of gray hair, his genial eyes gleaming through his gold-rimmed spectacles, his mild and rather hesitating speech—for he suffered from an impediment which had resulted from an early attack of chorea—were the appropriate outward signs of a nature whose leading traits were affection, devotion to the poor, and a steady, never-sleeping enthusiasm for his profession."

Finlay first published his belief in the mosquito transmission of yellow fever in a paper read before the Royal Academy in Havana on August 14th, 1881. His paper dealt with experiments started in June, 1881, with the mosquito now known as *Aëdes aegypti*. He went on with his experiments up to the time Reed started his work. He based his belief on a number of observations, such as the uncommon prevalence of this mosquito in yellow fever outbreaks. He pointed to the ecology of *A. aegypti;* that its habitat was at low altitudes, that it bred during warm weather, and that it was commonly

found in dwellings. All these were acute and pertinent observations. His experiments were based mainly on the hope that by mosquito inoculation a mild type of the disease would be produced, which would thus confer immunity. There is a record of 103 such experiments, according to Walter Reed. The tragedy is that although Finlay's faith in the mosquito theory was never shaken, the negative results of his own experiments were the strongest argument against his theory. "He hit upon the greatest discovery of the age but has never succeeded in demonstrating its truth," writes Mrs. Gorgas. In twenty years of repeated effort, he never once succeeded in producing a single case of yellow fever demonstrably produced by mosquito transmission. And so no one believed him, and the unbelievers included Gorgas and Walter Reed himself.

But there was about this time other support for the probability of an intermediate host in the propagation of yellow fever. Henry R. Carter, an officer in what is now the United States Public Health Service, then the United States Marine Hospital Service, working in Orwood and Taylor, Mississippi, in 1898 noted, as the result of many painstaking observations, that there was a difference in the periods which elapsed before an attack of the disease in the first case and in secondary cases. These periods are respectively about twelve and six days. He published his findings in the New Orleans Medical Journal, May, 1900. Mrs. Gorgas records that, when sent for publication, this paper was first rejected as being too long. The significance of Carter's observation was not recognized at the time. Yet it gave unmistakable pointers to two facts: That there must be an intermediate host, and that the intermediate host does not become infective until a period of about twelve days. This is what we call the extrinsic incubation period.

A characteristic of the epidemiology of yellow fever is that outbreaks are a direct function of the ingress of non-immunes. This was very clearly demonstrated in both Cuba and Panama.

The Cuban campaign started in June, 1900. A number of American troops and officials came to Havana — all non-immunes. Yellow fever broke out: 1,600 cases and 231 deaths in a few months. Consequently the Surgeon General, George M. Sternberg, himself a bacteriologist, appointed a board consisting of Walter Reed, James Carroll and Jesse W. Lazear, American officers, and Aristides Agramonte, a Cuban doctor, to study the causation and transmission of the disease. At the time Sanarelli's Bacillus icteroides was widely accepted as the causative organism of yellow fever.

By the way, that yellow fever was caused by an organism he named Paraplasma flavigenium was brought forward by Harold Seidelin of Liverpool at the 1912 Congress on Hygiene and Demography in Washington. The late Charles F. Craig, an eminent authority, said he thought the alleged Paraplasma were artifacts. So did I, when I saw the preparations at this meeting.

Later, in 1918, Noguchi claimed to have isolated an organism he called Leptospira icteroides, from the blood of yellow fever cases. This was another fallacy.

The work of the Board was therefore concentrated on isolating the organism from autopsy material and blood. All attempts were negative. Meanwhile, Finlay lost no time in speaking his theory to Reed. Walter Reed writes:

> "We here desire to express our sincere thanks to Dr. Finlay, who accorded us a most courteous interview and placed at our disposal his several publications relating to yellow fever during the past nineteen years."

However, I have it on unimpeachable authority that Reed did not believe Finlay's theory, and that he only undertook the experiments, which led to the complete vindication of Finlay, because he saw no other path open. Neither did Gorgas believe in the mosquito theory. Even after the conclusion of Reed's experiment, he wrote in his report, July 12th, 1902, to the Governor-General Wood, himself a physician:

> "This idea was so new and so entirely contrary to all former theories on the subject, and apparently to all former experiences, that the paper was received with scant belief. I myself had seen the work and was convinced that the mosquito could convey yellow fever, but I was hardly prepared to believe that it was the only way, or even the ordinary way of conveying the disease."

To us it may seem incredible that Finlay's theory, asserted with almost religious fervour, should have met with almost derision. To understand this, we must remind ourselves that when he first propounded his theory there was only one demonstration of the role of an intermediary host in disease transmission. That was Patrick Manson's discovery that filariasis was transmitted by a mosquito. This discovery was not at all well known outside a small circle of people. It was probably quite unknown to, or not believed by, those who disbelieved Finlay. This was the age of the new science of bacteriology with the strong partisanship that is a feature of a new discovery: People believed that there must be an organism which they could see, isolate in pure culture, cultivate, and reproduce the particular disease with this organism. Unsupported by the finding of any specific organism which corresponded to these criteria; on the basis only of observations of the presence of mosquitoes during yellow fever outbreaks, and that these outbreaks generally occurred during mosquito-breeding seasons, acknowledging that although he attempted to transmit yellow fever by mosquito bites in over a hundred experiments, he had no proof that he succeeded, Finlay inevitably at the best caused people to shrug their shoulders in disbelief, at the worst aroused lively antagonism and even derision.

In 1905, at the Pan American Medical Congress in Panama, Gorgas said—

"In time Reed's Army Board came along and made the astounding discovery that the mosquito alone conveyed yellow fever, and that dirt and filth had very little, if anything, to do with the question. My good friend, Dr. Finlay, some twenty years before had advanced this same theory, and, during the twenty years preceding our occupation of the island, had written and advocated the theory continuously. I had often heard him expound his views on the subject, but, like the Cuban woman, I smiled in a superior way at the 'crazy Cuban doctor.' "

But the "crazy Cuban doctor" kept at it for twenty long years and had the happiness of seeing not only his belief fully vindicated, but the application of his theory banish the dreaded disease from his own beloved Cuba and from all other urban areas where it lurked ready to strike chaos, dread and death.

Many honours came to Finlay. His Alma Mater conferred on him the honorary degree of LL.D. He was made an Honorary Fellow of the Philadelphia College of Physicians. He was the recipient of the Mary Kingsley Medal and was made an Honorary Member of the Liverpool School of Tropical Medicine. He was created an Officer of the French Legion of Honour, and also received the Breant Prize of the French Academy.

After his death on August 20th, 1915, a bust was unveiled in the Central Court of the Building of the Department of Public Health in Havana. Streets were named after him in Havana and Camaguey. A statue of him was erected in a square opposite the Public Health Department in Havana, in which there are also busts of Drs. Guiteras, Delgado, Gorgas and Lazear. The laboratory at St. Tomas' Hospital in Panama was named after him, and in 1927 The Finlay Institute for Research in Tropical and Preventive Medicine was established in Cuba. In the same year the Finlay Order of Merit was created in Cuba.

Various other honours came to him, and resolutions were passed at many scientific meetings paying homage to his achievements.

Perhaps it was at Jefferson, where Mitchell insistently taught, as did so many of his successors, that one must develop the power of observation, and not rest content with accepting Magister dixit, that the foundation was laid for Finlay's work and success, as the foundations were laid for the good work of many others in the long history of our College.

Of Finlay's life and work one can truly say in Kipling's words—

"For their work continueth,
And their work continueth,
Broad and deep continueth,
Greater than their knowing."